FORMULATION DEVELOPMENT AND EVALUATION OF BILAYER REGIO-SELECTIVE FLOATING TABLETS OF PROPRANOLOL HYDROCHLORIDE AND ROSUVASTATIN CALCIUM

A Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY
CHENNAI-32.

In partial fulfillment of the requirements for the award of degree of
MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted by
Register no: 261211255

Under the guidance of
Prof.K.Elango, M.Pharm. (Ph.D.)
Professor & Head
Department of Pharmaceutics

COLLEGE OF PHARMACY
MADRAS MEDICAL COLLEGE
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Evaluated

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Place: Chennai -03.

Date:

Dr.A.Jerad Suresh

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Place: Chennai -03.

Date:

Prof. K.Elango

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ABBREVIATIONS

GRDDS	- Gastro retentive drug delivery system
GIT	- Gastro intestinal tract
GRT	- Gastric emptying time
FDDS	- Migrating myoelectric complex
GFR	- Glomerular filtration rate
BMI	- Body mass index
HPMC	- Hydroxy propyl methyl cellulose
PVP	- Poly vinyl pyrrolidone
SSG	- Sodium starch glycolate
MMC	- Microcrystalline cellulose
IPA	- Isopropyl alcohol
PH	- Propranolol hydrochloride
RC	- Rosuvastatin calcium
RBFT	- Regio-selective bilayer floating tablet
SD	- Solid dispersion
IR-SD	- Immediate release solid dispersion compressed tablets
EC	- Ethyl cellulose
Mg	- Milligram
ml	- Milliliter
µg	- Microgram
%	- Percentage
RPM	- Revolution per minute
FTIR	- Fourier transform infra-red
RH	- Relative humidity

INDEX

INTRODUCTION

INTRODUCTION[1]

Oral route is the most widely used route of administration among all the routes that have been developed for systemic controlled delivery of drugs.

This is due to following reasons:

1. Oral route is most convenient and uncomplicated
2. Ease of administration and safe
3. Improved patient compliance
4. Cost-effective

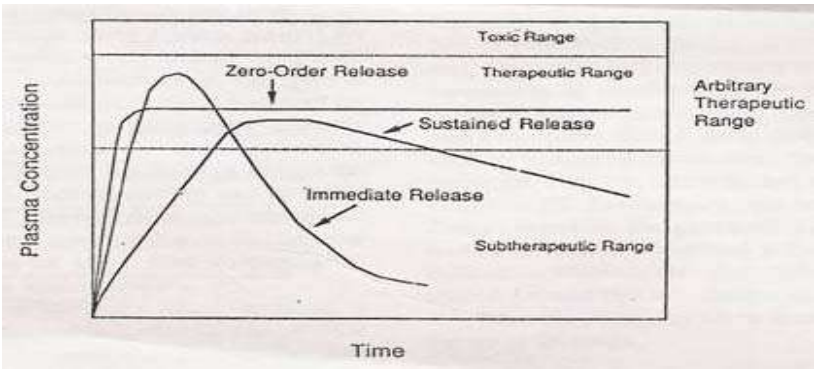
Oral solid dosage forms such as tablets and capsules have been formulated and developed nowadays since they are the most effective routes of administration of a new drug. Pharmaceutical products designed for oral delivery and currently available on the prescription and over the counter markets are mostly immediate release types, which are designed for immediate release of drug for rapid absorption. Many new generations of pharmaceutical products called controlled and sustained release drug delivery systems have also been developed. So the combination of both will be very much useful for immediate response and for maintaining the duration of action.

TABLETS

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. As per Indian pharmacopoeia, pharmaceutical tablets are solid, flat or biconvex, unit dosage form, prepared by compressing a drug or mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on the amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablet. Tablets are solid preparations each containing single dose of one or more active medicaments and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole or after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active medicament is liberated. They may have lines or break-

marks and may bear a symbol or other markings. Tablets may be coated or uncoated. They are sufficiently hard to withstand handling without crumbling or breaking

Fig 1: Plasma concentration – Time profile of conventional multiple dosing, single dose of sustained release and controlled release formulation



There are some limitations of conventional tablets. They are

- Drugs having short half-life require frequent administration
- The typical peak valley plasma concentration time profile of immediate release makes the attainment of steady state concentration difficult
- The fluctuations of drug concentration in plasma can lead to under medication or over medication
- The fluctuating drug concentration in plasma can lead to precipitation of adverse effects especially for a drug with small therapeutic index

CONTROLLED RELEASE DRUG DELIVERY SYSTEMS[2]

Controlled release drug delivery system was designed to deliver the for a prolonged period. Safe and effective blood levels are maintained for longer period as the system continues to deliver the drug. Controlled drug delivery usually results in constant blood levels of the drug as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient[2]

Advantages of controlled drug delivery systems

- Avoid patient compliance problems.
- Less total drug is used.
- Minimize local side effects and systemic side effects.
- Obtain less reduction in drug activity in chronic use.
- Minimize the drug accumulation with chronic dosing.
- Improve efficiency in treatment and cures the condition more promptly.
- Bioavailability of some drugs is improved.
- Make use of special effects, e.g., sustained release aspirin for morning relief of arthritis by dosing before bed.

Disadvantages

- Decreased systemic availability in comparison to immediate release formulation or conventional dosage forms, which may be due to incomplete release, increased first pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption,pH dependent stability etc.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
- Stability problems

GASTRORETENTIVE DRUG DELIVERY SYSTEMS[3]:

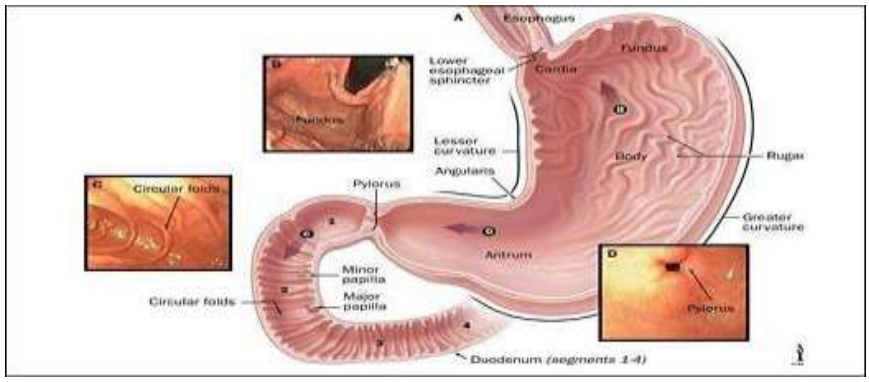
Oral controlled release dosage forms are developed due to their therapeutic advantages such as patient compliance, ease of administration and flexibility in formulation. However this approach has several physiological difficulties such as inability to locate the dosage form at the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying time. The gastric emptying time in human normally ranges from 2-3 hrs through which the major absorption zone (stomach and upper part of intestine) passes through.so the dosage form can result in incomplete drug absorption

from the delivery system and leading to reduced efficacy of the administered dose. Therefore, the control of placement of a drug delivery system in a specific region of the GIT offers greater advantage. The drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem in the intestine can be benefitted by this approach. These have led to the development of a unique oral controlled release dosage form with gastro retentive properties. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper GIT.

ANATOMICAL AND MECHANICAL ASPECTS OF THE STOMACH[4]:

A basic understanding of the anatomical and mechanical aspects of the stomach is needed for a pharmaceutical formulator to develop successful gastro retentive formulation .the stomach is divided into 4 regions – the cardia, fundus, body and pylorus. Gastric emptying occurs both during fasted and fed states. The pattern differs in two states. In the fasted state, the pattern is characterized by a series of motor activities known as inter- digestive myoelectric cycle or Migrating Motor Complex (MMC) which usually occurs every 80-120mins.

Fig 2: Anatomical representation of the stomach



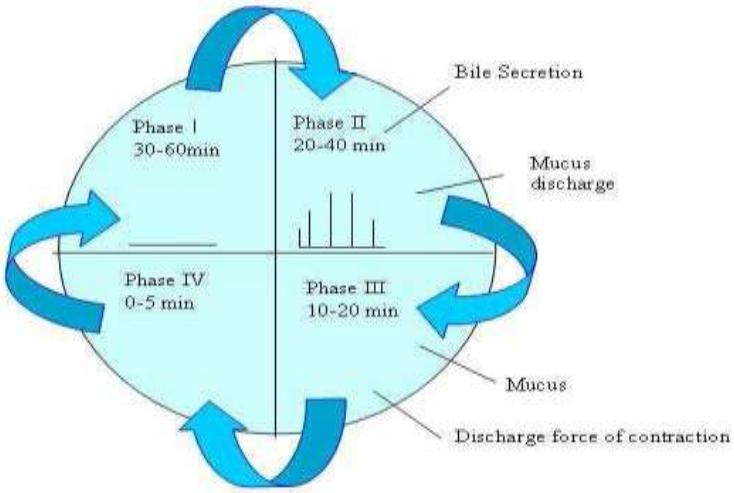
Gastric emptying is divided into 4 phases are as following:

This is called the inter-digestive myloelectric cycle or migrating myloelectric cycle (MMC) which is further divided into following 4 phases as described by Wilson and Washington.

MMC phases

Phase	**Time**	**Type**
I (basal phase)	Lasts from 40 to 60 Minutes	With rare contractions.
II (pre-burst phase)	lasts for 40 to 60 minutes	with intermittent action potential And contractions.
III (burst phase)	lasts for 4 to 6 minutes	intense and regular contractions for Short period.
IV (digestive motility pattern)	lasts for 0 to 5 minutes	continuous contractions

Fig 3: Motility patterns of the GIT in the fasted state



Influencing factors over gastric retention physicochemical factors:

- Density
- Size
- Shape of dosage form
- Food and drug interactions e.g., Anticholinergic agents (e.g., atropine, propantheline) opiates(e.g., codeine)
- Prokinetic agents (e.g. Metoclopramide, cisapride)

Biological factors:

- Gender
- Posture
- Age
- Body mass index
- Disease states(e.g., diabetes, crohn's disease)

Details are as follows:

- Density
    - The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm / cm3 is required to exhibit floating property.

- Food
    - Food affects the GRT of dosage forms depending on its nature, caloric content, and the frequency of intake.
- Nature of meal-feeding of indigestible polymers or fatty acid salts can change the motility pattern of stomach to a fed-state, thus decreasing the gastric emptying rate and prolonging drug release.

- Caloric content-GRT can be increased by 4-10 hours with a meal that is high in proteins and fats.
- Frequency of feed- The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of myoelectric motor complex.
- Size
    - Small-size tablets are emptied from the stomach during the digestive phase, while larger units are expelled during housekeeper waves. Floating units with a diameter equal to or less than 7.5mm had longer GRTs compared to non-floating units. GRT were similar for floating and non-floating units having a larger diameter of 9.9mm.
- Shape
    - Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.

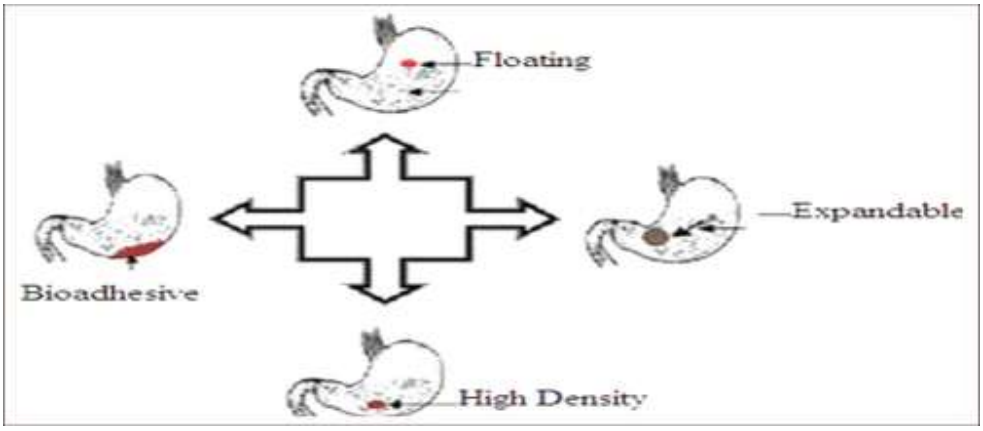
- Gender
    - Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface)

- Posture
    - The mean GRT for volunteers in the supine state was not significant from that in the upright, ambulatory state.

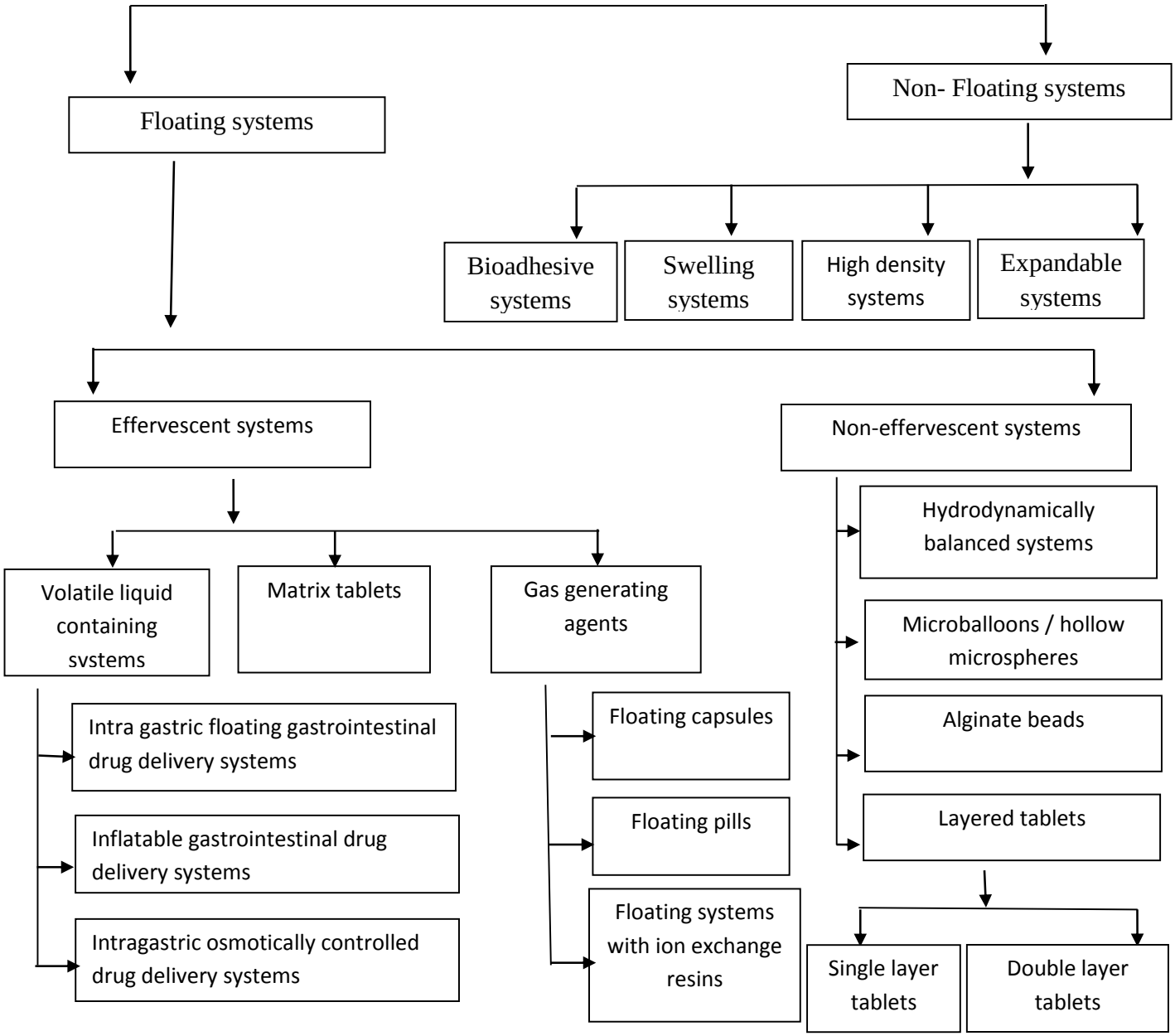
- Fed or unfed state – under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

- Age – elderly people, especially those over 70, have a significantly longer GRT.

Fig 4: Mechanism of gastro-retention of the drug



GASTRORETENTIVE DRUG DELIVERY SYSTEMS[5]



REGIO-SELECTIVE FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery system or hydro dynamically balanced systems have a bulk density lower than gastric contents and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in plasma drug concentrations.

However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal.

To measure the floating force kinetics, a novel apparatus used for determination of resultant weight (RW). The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side.

Advantages of Floating drug delivery system[6]

A floating drug delivery system offers numerous advantages over conventional drug delivery System:

Sustained drug delivery A floating drug delivery system can remain in the stomach for several hours and the assumed prolongation in the gastric retention is postulated to cause sustained drug release behavior.

Site-specific drug delivery Targeting of drug to stomach appears to be useful for all substances intended to produce a lasting local action on the gastro duodenal wall.

Pharmacokinetic advantage In addition, with the total gastrointestinal transit duration is increased, a greater amount of drug may be delivered and thus the relative bioavailability will consequently be increased

Targeted therapy for local ailments in the upper GIT The prolonged and sustained

administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. Eg. Antibiotic for Helicobacter pylori based ulcer, Antacid.

Reduced counter-activity of the body Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

Minimized adverse activity at the colon Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented.

Enhanced bioavailability The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations.

Disadvantages of floating drug delivery system

Floating system is not feasible for those drugs that have solubility or stability problem in G.I.Tract.

These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water. The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

Three major requirements of FDDS are

- It must form a cohesive gel barrier.
- It must maintain specific gravity lower than gastric contents (1.004-1.01g//c).
- It should release contents slowly to serve as a reservoir.

Criteria for selection of drug candidate for FDDS

Desirable half-life If the drug has a short half-life of less than 2 hours, the dosage form may contain a prohibitively large quantity of the drug.

High therapeutic index Drugs with low therapeutic index are not suitable for incorporation in controlled release formulations. e.g. Digitoxin.

Small dose the dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undermined

Aqueous solubility Drugs with aqueous solubility make good candidates for controlled release dosage form.

Stability to wide pH range, GI enzymes and flora Stability of the drug in the GI contents is important to ensure a complete and reproducible drug input into the body. Typically the drug must be stable in the pH range of 1 to 8.

First pass clearance Delivery of the drug to the body in desired concentration is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release form. Saturable hepatic metabolism may render a drug unsuitable because systemic availability for such drug is highly reduced when the input rate is small.

Drugs those are Unsuitable for Gastro retentive Drug Delivery Systems

- Drugs that have very limited acid solubility e.g. phenytoin etc.
- Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
- Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

Classification of FDDS[7]

A. Single Unit Floating Dosage Systems

a) Effervescent Systems (Gas-generating Systems)

b) Non-effervescent Systems

B. Multiple Unit Floating Dosage Systems

a) Non-effervescent Systems

b) Effervescent Systems (Gas-generating Systems)

c) Hollow Microspheres

d). Raft Forming Systems

Types of floating drug delivery system

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS

(A). Non-Effervescent FDDS

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in noneffervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol.

The various types of this system are as:

(1). Colloidal gel barrier systems

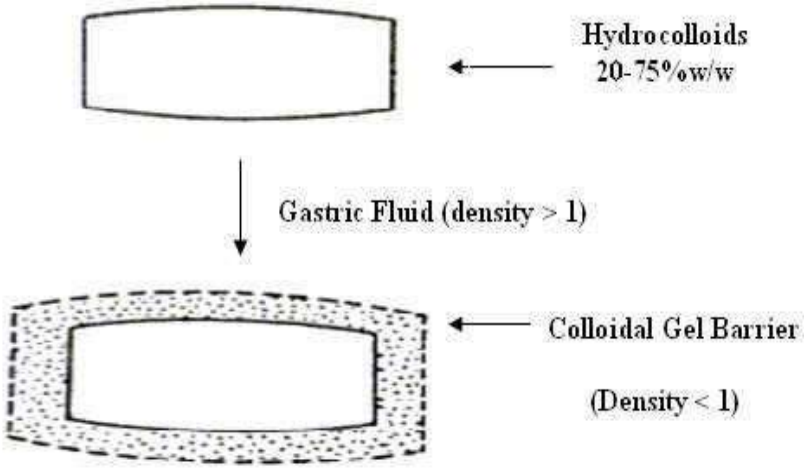
Hydro-dynamically balanced system (HBS) of this type contains drug with gel forming or Swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers. They help in prolonging the GI residence time and maximize drug reaching its absorption site in the solution form ready for absorption. These systems incorporate high levels (20 to 75 %

w/w) of one or more gel forming highly swellable cellulose type hydrocolloids e.g. Hydroxyethyl cellulose, hydroxyropyl cellulose, hydroxyropyl methyl cellulose, sodium carboxymethylcellulose incorporated either in tablets or capsules.[60]

(a). Single Layer Floating Tablets: They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

(b). Bi-layer Floating Tablets: A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

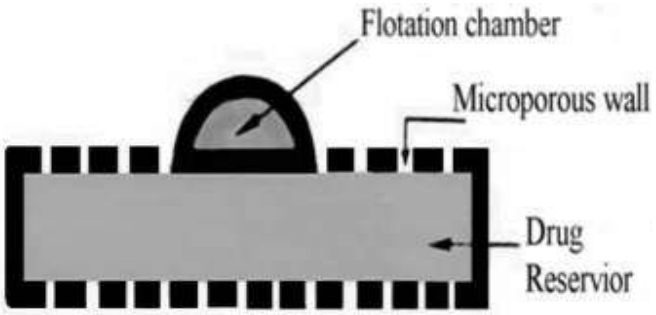
Figure 5: Intragastric floating tablet.



(2). Micro porous compartment system

This technology is comprised of encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom surfaces. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric mucosal surface with undissolved drug. In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the pores, dissolves the drug and carries the dissolved drug for continuous transport across the Intestine for absorption.

Figure 6: Micro porous intra-gastric floating drug delivery device



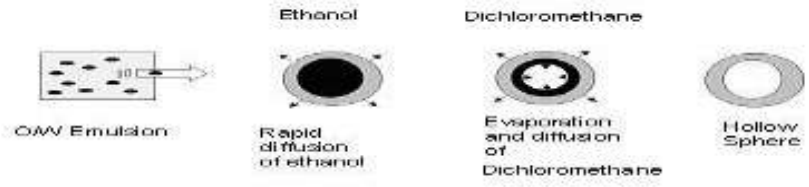
(3). Alginate Beads

Multi-unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

(4). Hollow Microspheres

Hollow microspheres (Microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40 °C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The Microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.

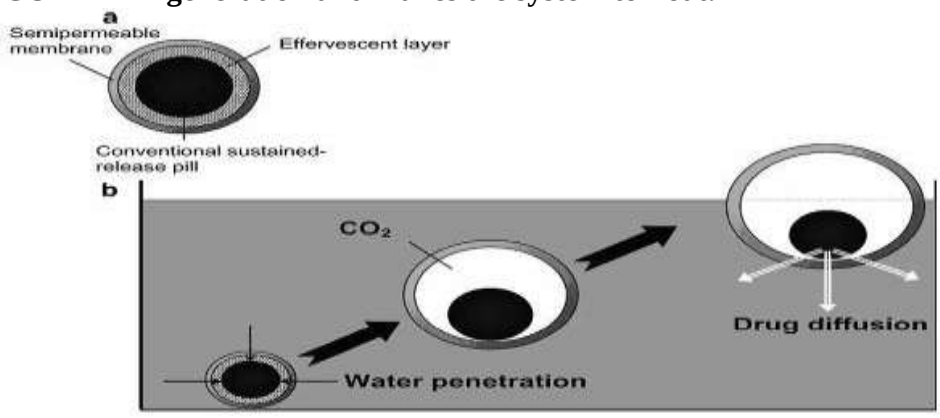
Fig 7: Mechanism of micro balloon formation by emulsion-solvent diffusion Method.



(B) Effervescent FDDS[8]

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts.

Fig 8: Floating pills a) The penetration of water into effervescent layer leads to a CO2 generation and makes the system to float.



(1) Volatile liquid containing system

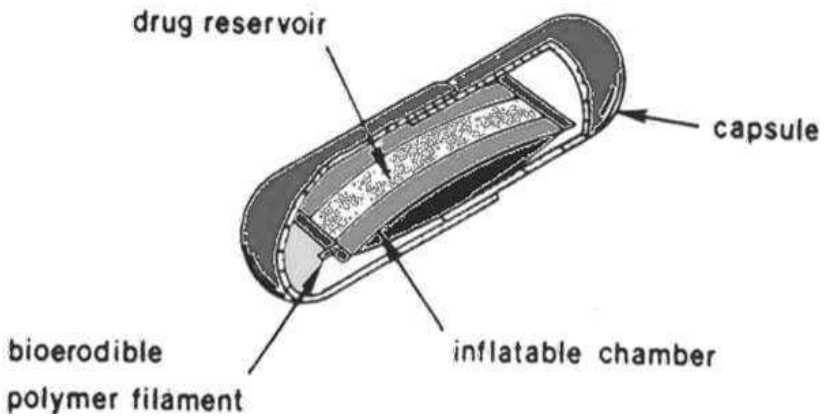
The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a

predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach[9.]

(a) Inflatable gastrointestinal delivery systems

In these systems an inflatable chamber is incorporated, which contains liquid that gasifies at body temperature to cause the chamber to inflate in the stomach. The inflatable chamber automatically inflates and retains the drug reservoir compartment in floating position. The drug continuously released from the reservoir into the gastric fluid.

Fig 9: Inflatable gastrointestinal delivery system



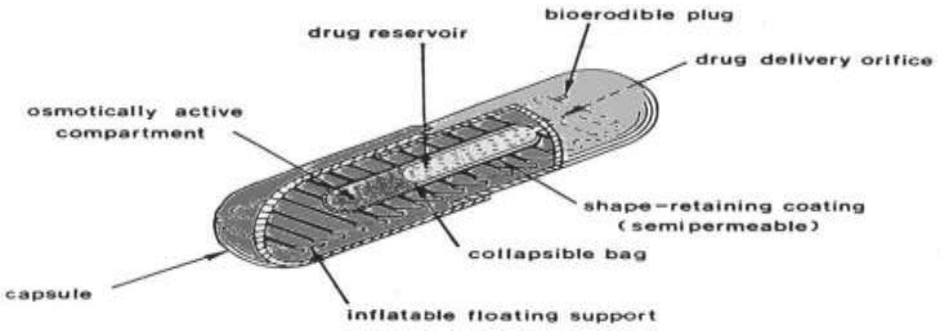
(b) Intragastric osmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible

bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and turns in forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release in solution form through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach

Fig 10: Intragastric osmotically controlled drug delivery system



(2) Gas-generating Systems*:*

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime.

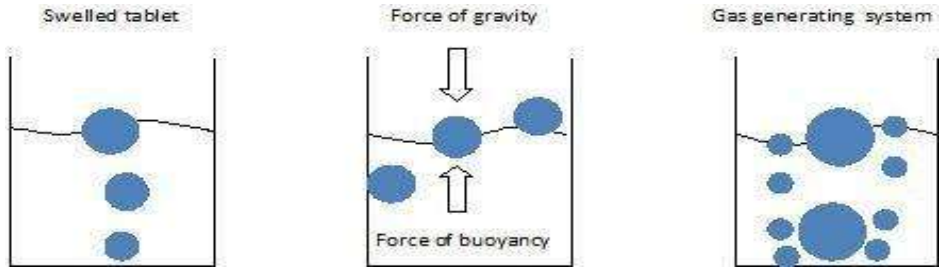
(3). Raft Forming systems

Here, a gel-forming solution (e.g. Sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles on contact with gastric fluid. Formulations also typically contain antacids such

as aluminum hydroxide or calcium carbonate to reduce gastric acidity.

Because raft forming systems produce a layer on the top of gastric fluids, they are often used for gastro-oesophageal reflux treatment as with Liquid Gaviscon (GlaxoSmithKline).

Fig 11: Mechanism of floating drug delivery system



The magnitude and direction of force/resultant weight (up or down) is corresponding to its buoyancy force ($F_{buoyancy}$) and gravity force ($F_{gravity}$) acting on dosage form

$$F = F_{buoyancy} - F_{gravity}$$

$$F = D_f g V - Ds g V$$

$$F = (D_f - Ds) g V$$

$$F = (D_f - M/V) g V$$

Where,

F = resultant weight of object

D_f = Density of Fluid

DS = Density of Solid object

g = Gravitational force

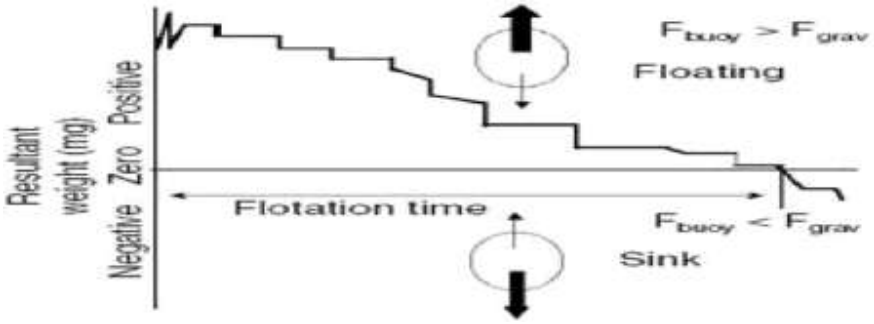
M = Mass of dosage form

V = Volume of dosage form

So when Ds, density of dosage form is lower, F force is positive gives buoyancy and when it is Ds is higher, F will negative shows sinking.

Plot of F vs. Time is drawn and floating time is time when F approaches to zero from positive values.

Fig 12: Effect of buoyancy force and gravity force on drug delivery system



Effervescent (gas generating) systems

Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent Components (e.g. sodium bicarbonate, citric acid or tartaric acid). The optimal stoicheometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. In this system carbon dioxide is released and causes the formulation to float in the stomach.

Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) coated with hydroxyl propyl methylcellulose (HPMC), and floating system based on ion exchange resin technology.

Bilayer or multilayer system has also been designed. Drugs and excipients can be formulated independently and the gas generating material can be incorporated into any of the layers. Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide.

NON-FLOATING SYSTEMS

These are another class of gastroretentive drug delivery systems which do not float but remain in the stomach for a prolonged time period. These systems are formulated by any of the following approaches.

i. Bioadhesive systems: These types of systems adhere to the biological membrane (mucosa) of the stomach and maintain intimate contact with the membrane for a longer time and hence retains in stomach for its prolonged release. These systems are formulated using Bioadhesive polymers which can adhere to epithelial surface in the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc.

ii. Swelling systems: These are a type of non-floating gastroretentive drug delivery system which when enters stomach swells (due to presence of swellable polymers) to an extent that cannot pass through the pyloric sphincter leading to its retention in the stomach.

iii. High density systems: These systems possess density greater than the gastric fluids due to which the system sinks to the bottom and remains in the stomach. These are formulated by coating drug on heavy inert materials like zinc oxide, titanium dioxide, iron powder, etc.

iv. Expandable systems: These systems are capable of expanding and retain in the stomach for longer periods. These are usually formulated as a capsule containing dosage form in folded and compact form. After being exposed to stomach environment, capsule shell disintegrates and dosage form expands preventing its exit through the stomach. By using a suitable polymer, sustained and controlled drug delivery can be achieved.

Evaluation for gastro retention is carried out by means of

- X-ray
- Gamma scintigraphic monitoring of dosage form transit in the GI tract

Generally manufactured marketed products[10]:

Table 1: Generally manufactured marketed products:

S.No	Brand name	Drug dose	Company and country	Remarks
1	Valrelease	Diazepam 15 mg	Roche, USA	Floating capsule
2	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming tablets
3	Liquid gavison	Aluminium hydroxide and mg. carbonate	GlaxoSmithKline, UK	Effervescent Floating liquid alginate
4	Topalkan	Aluminium-Magnesium antacid	Pierre-Fabre, Drug	Floating liquid alginate

Polymers and Other Ingredients Used In preparations of Floating Drugs[11, 12]

The following types of the ingredients can be incorporated in to FDDS

Hydrocolloids: Suitable hydrocolloids are synthethics, anionic or non-ionic like hydrophilic gumes, modified cellulose derivatives.

Example: Acacia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, HPMC K4 M, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate, Methocel K4M.

Polyethylene oxide, β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbonate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4 M and Carbopol can be used.

LITERATURE REVIEW

LITRATURE REVIEW

1) **Modi Foram P *et al.*,** [13] formulated and evaluated fixed dose combination moisture barrier film coated bilayer tablet of artesunate and amodiaquine hydrochloride. The tablets were prepared by dry granulation method for artesunate and wet granulation method for amodiaquine hydrochloride. The formula of amodiaquine hydrochloride was optimized using PVPK-30 as a binder.

2) **Durga Prasad Patnayak *et al*.,**[14] prepared bilayer tablet formulation of metformin hydrochloride and glimepiride Two different matrix formulations were developed, one matrix layer with hydrophilic swellable polymer and another with hydrophobic polymer as carriers for sustained drug delivery from matrices and were evaluated. Hydroxypropylmethylcellulose and Polyethylene oxide was used as polymers in order to get the sustained release profile over a period of 24 h. Tablet s were evaluated for physical properties; drug content and in vitro drug release were compared with standard commercial tablet s (Glimy-M). The excipient s used in this formulation did not alter physicochemical properties of drug, as tested by HPLC, DSC, and FTIR. Stability of the drug release profiles at 6 months in 40◦C and 75%RH suggesting that HPMC based sustained release formulation was stable than the Polyethylene oxide sustained release formulation due to its stable and better targeting profile in terms of drug release.

3) **Mina Ibrahim Tadros *et al*.,** [15] developed controlled-release effervescent floating matrix tablets of Ciprofloxacin hydrochloride with swelling, floating and adhesive properties. Ten tablet formulations were designed using HPMC K15M and/ or sodium alginate as release-retarding polymer(s) and sodium bicarbonate or calcium carbonate as a gas former. Swelling ability, floating behavior, adhesion period and drug release studies were conducted in 0.1N HCL ($P^{H\ 1.2}$) at 37±0.5°c. The tablets showed acceptable physicochemical properties. Drug release profiles of all formulae followed non-Fickian diffusion. Statistical analyses of data revealed that tablets containing HPMC K15M (21.42%w/w), sodium alginate (7.14%w/w), and sodium

bicarbonate(20%w/w) (formula F7) or $CaCO_3$ (20%w/w) (formula 10) were promising systems exhibiting excellent floating properties, extended adhesion periods and sustained drug release characteristics.

4) **Swain K *et al.,*** [16] developed controlled release Gastro retentive floating drug delivery system of Theophylline by employing response surface methodology. A 3^2 randomized full factorial design was developed to study the effect of formulation variables like various viscosity grades and contents of HPMC. The floating lag time for all nine experimental trial batches were less than 2 min and floatation time of more than 12 h. Theophylline release from the polymeric matrix system followed non-Fickian anomalous transport. Multiple regression analysis revealed that both viscosity and content of HPMC had statistically significant influence on all dependent variables.

5) **Muthukumaran M *et al.,*** [17] fabricated and evaluated of sustained release mucoadhesive bilayer tablets containing Nifedipine using the Natural Bioadhesive polymers such as Pectin to compare the synthetic polymer like Carbopol 971-P, HPMC-K4M and Polyvinyl pyrrolidone (PVP- K30) along with ethyl cellulose and magnesium stearate as an impermeable backing layer to improve the oral bioavailability. The pre formulation study was performed by FTIR and DSC. The first layer which adheres to mucosa was obtained by direct compression of mucoadhesive polymers and drug. The second layer containing water impermeable agent was compressed on the first layer. The tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, swelling index, in vitro drug release. The surface pH of all the tablets was close to neutral pH the mechanism of drug release was found to be non-fickian diffusion.

6) **Mujoriya R Z *et al.***, [18] developed and evaluated metoprolol succinate er and amlodipine besilate bilayer tablet by using different polymer (HPMC, Methocel,

Carbapol) with different diluents (MCC, Cellulose Phosphate, Starch, Croscarmalose Sodium) and then evaluated. The experimental work was divided into Preformulation studies, formulation development and evaluation. Standardization of drug and excipients confirmed the authentication of the samples. Thus it can be concluded that a stable bilayer tablet of Metoprolol succinate ER and Amlodipine besilate can be prepared by using HPMC K 15 M and carbomer as a polymer. It was found that the in vitro drug release of Metoprolol succinate ER was best explained by first order (r2 =0. 9994), as the plots showed the highest linearity, followed by Higuchi's equation (r2 = 0.9974) and zero-order (r2 = 0.9471).

7) **Akash Yadav *et al.,*** [19] developed a bilayer and Floating-Bioadhesive drug delivery system exhibiting a unique combination of floatation and bio adhesion to prolong residence in the stomach using propranolol hydrochloride as a model drug. The sustained layer was compressed and granules of the floating layer were added to it then both layers were compressed using a single station rotary press. Hydroxypropyl methylcellulose (HPMC) and sodium bicarbonate were added to the floating layer and, when immersed in 0.1 mol/ l HCl, the tablet expands and rises to the surface where the drug is gradually released without interference from gas bubbles. The in vitro drug release from the tablet was controlled by the amount of HPMC in the sustained release layer. The floating ability of the tablets was studied. The concentration of HPMC significantly affects the drug release rate, buoyancy lag-time, detachment force and swelling characteristics of the tablets. The tablet was buoyant for up to 8 h. This kind of tablet exhibits independent regulation of buoyancy and drug release.

8) **Jain Jitendra *et al.,*** [20] was developed a bilayer-floating tablet (BFT) for Indomethacin using direct compression technology. Bilayer tablets were punched using optimized solid dispersion, HPMC K4M, Avicel PH-112, ac-di-sol, magnesium stearate and aerosil in fast release layer and optimized floating layer as sustained release layer. Tablets were evaluated for physic -Chemical properties such

as Hardness, Friability, Thickness, weight Variation and drug content uniformity. FT-IR studies are performed. In Vitro dissolution studies were carried out in a USP type II Paddle type apparatus. The optimized formulation (A2) showed no significant changes on stability studies when storing at 4º c, 40º c, /75%RH, 60ºc/80% RH for 3 months. The release data obtained from the dissolution study of the bilayer tablets were analyzed with respect to first order model, Higuchi model, Korsmeyer-Peppas model, and zero order models. In this study optimized formulation (A2) release the drug up to 24hrs.

9) **Ajit Kulkarni *et al.,*** [21] prepared the regio-selective bilayer floating tablets of Atenolol and Lovastatin for biphasic release profile by direct compression technique. The bilayer floating tablets comprised of two layers, immediate release layer of sodium starch glycolate as a super disintegrant and the sustained release layer comprised of Hydroxy propyl methyl cellulose (HPMC) K100M and xanthan gum as the release retarding polymers. Sodium bicarbonate was used as a gas generating agent. All formulations formulated for more than 12 hours and released 90% of lovastatin within 30 min. Roentgenography was carried out to study the *in vivo* buoyancy of the optimized formulation and it was found to be buoyant for 8 hour in stomach.

10) **Ziyaur rahman *et al.,*** [22] developed the bilayer- floating tablets of captopril using direct compression method. The floating layer was formulated with HPMC K- grade (K4M, K15M and K100M) and effervescent mixture of citric acid and sodium bicarbonate. The sustained release layer comprised of captopril and various polymers such as HPMC- K15M, PVP-K30 and Carbopol 934p alone or in combination with the drug. Final formulation released approximately 95% of drug in 24 hours *in vitro*, while the floating lag time was 10 min and the tablet remained floatable throughout the studies. Placebo formulation containing barium sulphate in the release layer administered to human volunteers for *in vivo* X – ray studies showed that BFT had significantly increased the gastric residence time.

11) **Shweta sharma *et al.,*** [23] studied the formulation and evaluation of gastro-retentive floating matrix tablet of captopril. The floating tablets were prepared by direct

compression method using HPMC K4M, HPMC K15M and HPMC K100M. Sodium bicarbonate was used as a gas generating agent. The optimized formulation showed floating for more than 8 hours and retarded the release for more than 10 hours.

12) **Arunachalam.a *et al.,*** [24] prepared levofloxacin hemihydrate floating tablets by melt granulation method using the polymer, hydroxy propyl methyl cellulose (HPMC K100M) with different amounts and other excipients and sodium bicarbonate as gas generating agent. They developed a floatable drug delivery system of Levofloxacin hemihydrate for sustained drug delivery and gastric retentive property with special emphasis on optimization of formulations for floating matrix tablets. Levofloxacin floating tablet drug delivery system showed improved in-vitro bioavailability and extended drug release which may favour the reduced dose frequency and patient compliance.

13) **Venkata Srikanth Meka *et al.,*** [25] investigated the formulation of gastro retentive floating drug delivery system s (GRFDDS)of propranolol HCl by central composite design and to study the effect of formulation variables on floating lag time, D 1hr (% drug release at 1 hr.) and t90 (time required to release 90% of the drug). 3 factor central composite designs were employed for the development of GRFDDS containing novel semi synthetic polymer carboxymethylethyl cellulose (CMEC) as a release retarding polymer. CMEC, sodium bicarbonate and Povidone concentrations were included as independent variables. Optimized formulation was selected based on the criteria of less than 20 % of the drug release at 1 hr (fixed by USP dissolution conditions) and 90% of the drug released in between 10 to 11 hrs.

14) **Swati C. Jagdale *et al.,*** [26] developed a gastro-retentive drug delivery system of propranolol hydrochloride. The ability of various polymers to retain the drug when used in different concentrations was investigated. Hydroxypropyl methylcellulose (HPMC) K4 M, HPMC E 15 LV, Hydroxypropylcellulose (HPC; Klucel HF), xanthan gum, and sodium alginate (Keltose) were evaluated for their gel-forming

abilities. The bioavailability of propranolol increases in presence of food. Also, the absorption of various drugs such as propranolol through P-glycoprotein (P-gp) efflux transporter is low and erratic. They were evaluated for physical properties, in vitro release as well as in vivo behavior. In preliminary trials, tablets formulated with HPC, sodium alginate, and HPMC E 15 LV failed to produce matrix of required strength, whereas formulation containing xanthan gum showed good drug retaining abilities but floating abilities were found to be poor. Finally, floating tablets were formulated with HPMC K4 M and HPC.

15) **Arun Prasad K *et al.,*** [27] formulated solid dispersion tablet of Terbinafine Hydrochloride using carriers polyethylene glycol 6000 (by melting method) and polyvinyl pyrrolidone K 30 (by solvent method) in the drug carrier ratio of 1:1, 1:2 and 1:3. The prepared solid dispersions were characterized for their drug content, thermal studies, infrared spectral studies, differential scanning calorimetric studies, aqueous solubility studies and in-vitro release studies. As a result solid dispersion formulation showed improved dissolution rate than pure drug and physical mixture. The solid dispersion showing better release profile was chosen to formulate into a tablet dosage form of weight 600 mg. The tablets compressed were evaluated for its physical parameters. The dissolution profile of formulated tablet was compared with the marketed product and the formulated tablet showed better release profile than the marketed product.

16) **Ganesh Chaulang *et al.,*** [28] enhanced the dissolution profile of furosemide using solid dispersion (SD) with crospovidone (CPV) by kneading technique. 1:1 (w/w) and 1:2 (w/w) solid dispersions were prepared by kneading method using solvent water and ethanol in 1:1 ratio. Dissolution studies using the USP paddle method were performed for solid dispersions of furosemide at 37 ± 0.5^{o}C and 50 rpm in simulated gastric fluid (SGF) of pH 1.2. Fourier transformer infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and x-ray diffractometry (XRD) were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. Tablets were compared with commercial

products. Dissolution of furosemide improved significantly in solid dispersion the 1:2 solid dispersion indicated increase in dissolution 5.11 fold. Tablets containing solid dispersion exhibited better dissolution profile than commercial tablets.

17) **S Vidyadhara *et al.*,** [29] prepared Solid dispersions of Glimepiride with sodium starch glycolate (SSG) and further compressed as tablets using diluents such as lactose, dicalcium phosphate and microcrystalline cellulose. The solid dispersions of Glimepiride with SSG at different ratios were prepared by physical mixing, solvent evaporation and kneading methods. The rapid release of poorly soluble Glimepiride from solid dispersions was influenced by the proportion of polymer and the method employed for its preparation. The solid dispersions exhibit faster dissolution characteristics as compared to plain drug. This was due to solubilizing effect of carrier or crystallization of drug entrapped in molecular state by the carrier. A higher dissolution rate was obtained with solid dispersions prepared by solvent evaporation method and kneading method in the ratio of 1:2 for the drug and SSG.

18) **K P Chowdary *et al.*,** [30] formulated and evaluated etoricoxib solid dispersion using starch phosphate, PVP and PEG 4000 by factorial design for enhancing the dissolution rate and efficiency of etoricoxib, a BCS class II drug. The individual main and combined effects of the three factors namely starch phosphate (factor A), PVP K- 30 (factor B) and PEG 4000 (factor C) in enhancing the dissolution rate and dissolution efficiency of etoricoxib were evaluated in a 23- factorial study. DE30 was also increased from 3.03% for etoricoxib pure drug to 55.28, 46.36 and 36.61 % respectively with solid dispersions. Addition of PVP and PEG 4000 to the solid dispersions in starch phosphate has further increased the dissolution rate upto 200.59 fold and dissolution efficiency upto 29.15 fold.

19) **Anusha P *et al.*,** [31] developed and evaluated Drotoverine taste masked tablets with improved dissolution efficiency using solid dispersion technique. The purpose of his

research work is to mask the bitter taste of the drug and formulate the taste masked solid dispersion of the drug into tablets by direct compression method. Solid dispersion prepared by using urea and mannitol by melting / fusion method. An *In vitro* release study also performed. In addition to taste masking the tablets exhibits better dissolution profile.

20) **Sharmi Islam *et al.*,** [32] studied the enhancement of dissolution rate of gliclazide using solid dispersion method. The solid dispersion prepared by using poloxamer by solvent evaporation method. The solid dispersions are evaluated for the drug loading and dissolution behavior and were found effective to enhance the solubilty of gliclazide in dissolution medium significantly.

21) **Panikkarakayil Habeeb *et al.*,** [33] formulated, optimized and evaluated solid dispersion tablets of aceclofenac using Kollidon 30. From this study they evaluated the effect of polyvinyl pyrrolidone on dissolution enhancement of aceclofenac from solid dispersion both by *invitro* and *invivo* methods. Aceclofenac solid dispersion exhibited considerable increase in the solubility in comparison with the pure drug in 7.4 pH phosphate, methanol, isopropyl alcohol and acetone. It is noted that the quantity of the carrier have considerable effect in the solubility of the drug in the solid dispersion. It is concluded that the dissolution of aceclofenac can be enhanced by the use of hydrophilic carrier like PVP.

22) **D V Pawar *et al.*,** [34] formulated and evaluated controlled release matrix tablet with solid dispersion granules of aceclofenac. The tablets were prepared by direct compression method using polymers like HPMC, Carbopol 934(CP). This formulation contains 25% of HPMC has complete release of 24 hours as well as CP containing formulations showed concentration dependent rate of drug release. It is clarified that solid dispersion granules was one of the promising controlled release system applying solid dispersion technique for the poorly water soluble drug.

23) **Abdul Althaf S *et al.,*** [35] formulated and evaluated the bilayer immediate release tablets of clopidogrel biphosphate and aspirin. This study was intended to produce an immediate release bilayer tablets using solid dispersion technique. The prepared tablets were evaluated for the dissolution. The dissolution followed zero order kinetics as it is independent of concentration. Fusion method was employed for preparing solid dispersion as it improves safety and efficacy and intern improves its bioavailability. Formulations F2, F3, F4 were taken to study the effect of superdisintegrants like sodium starch glycolate, crospovidone, Croscarmalose sodium respectively. 6% superdisintegrants concentration showed better release profile compared with other concentrations.

24) **Pankaj Nainwal *et al.,*** [36]. performed a comparative solubility enhancement study of rosuvastatin using solubilization techniques Solid dispersion of Rosuvastatin was prepared by solvent evaporation method; PEG (Polyethylene glycol) 4000, mannitol and urea were used as carriers. The solubility enhancement of Rosuvastatin by different solubilization technique was observed in decreasing order as hydrotropic solubilization > solid dispersion > Micellar solubilization. It was observed that the solubility increased with the increase in the concentration of hydrotropic agents and amongst the various hydrotropic agents used the solubility was Rosuvastatin was enhanced greatest to 55 folds with sodium salicylate.

25) **S H Lakade *et al.,*** [37] formulated and evaluated sustained release matrix tablet of Anti-anginal drug. The objective of study was the development of hydrophilic polymer (HPMC) and hydrophobic (EC) based nicorandil matrix sustained release tablet which can release the drug upto time of 24 hours in predetermined rate. The in-vitro release rate profile should the higher concentration of F2 polymer in tablet, the combination of hydrophilic and hydrophobic combination showed less result

than use of alone. The in–vitro release data was well fit to Peppas and Hixon crowel release kinetics.

26) **Patel R *et al.*,** [38]optimized propranolol hydrochloride controlled release matrix tablet by using factorial study design prepared by direct compression technique.Hydroxypropylmethylcellulose K15M, (HPMC K15M) and Carbopol 934P were used in formulating the matrix tablets. The results indicate that batch F7 showed the highest value among all the batches. It was observed that the blending ratio of HPMC K15M-Carbopol 934P and polymer concentration have distinct effect on in-vitro drug release profile. Release rate of Propranolol hydrochloride decreased proportionally with increased in concentration of Carbopol 934P and total polymer concentration.

27) **Kiran Chaturvedi *et al.*,** [39]formulated and performed *invitro* evaluation of propranolol floating matrix dosage form developed by direct compression method using citric acid and sodium bicarbonate as the effervescent base. Hydroxypropyl methylcellulose; HPMC K15M was used to prepare the floating tablets to retard the drug release for 12h in stomach. Na-carboxy methyl cellulose (NaCMC) or carbopol 934P was added to alter the drug release profile or the dimensional stability of the formulation. Formulations were evaluated for floating lag time, duration of floating, dimensional stability, drug content and in vitro drug release profile. Formulation F5 containing a combination of carbopol and HPMC was able to maintain a firm matrix, showed good water uptake and was able to sustain the drug release and only 87.16% drug was released at the end of 12 h.

28) **Nitya Sri Valli Ruthraraju *et al.*,** [40] prepared rosuvastatin calcium nanoparticles by top down and bottom up techniques; the top down technique produced particles in the nanometer size range of below 1000nm. The Nano crystal formulations F-3, F-4, F-5 prepared by top down technique using polymeric and surfactant stabilizers shows that particles size was within the nanometer range.

Formulations containing PVP, SLS, Poloxamer 188, Tween 80: PVP, and Tween 80: HPC as polymeric and surfactant stabilizers were prepared and compared. HPC and HPMC containing formulations were found to give better release of drug.

29) **Shaimaa N Abd Al Hammid *et al.,*** [41] developed Orodispersible tablets of Rosuvastatin using different types of superdisintegrants to enhance the disintegration and dissolution of Rosuvastatin to improve bioavailability of the drug. Formulas prepared by direct compression showed good flowability, while formulas prepared by wet granulation showed very poor flow properties. Various superdisintegrants were used including Croscarmalose (CCS), sodium starch glycolate (SSG) and crospovidone (CP), the latter found to be the best in term of showing the fastest disintegration time.

30) **Shantveer V Salger *et al.,*** [42] prepared and evaluated sustained release matrix tablets of propranolol hydrochloride. Hydroxypropyl methyl cellulose K100M used as a rate retarding polymer whereas lactose and dibasic calcium phosphate are used as diluent. The effects of the proportion of the polymer and the influence of co-excipients like lactose and dibasic calcium phosphate on the release rate of drug was investigated. The dissolution t50% and t90%values for the co-excipients were in the order of lactose>dibasic calcium phosphate. On conclusion The drug-polymer ratio was found to influence the release of drug from the formulations. As the polymer level is increased, the drug release rates were found to be decreased.

31) **Shivanand Pandey *et al.,*** [43] formulated and evaluated Gastro retentive tablets of propranolol hydrochloride by direct compression method using citric acid and sodium bicarbonate as the effervescent base. Hydroxypropyl methylcellulose; HPMC K15M was used to prepare the floating tablets to retard the drug release for 12h in stomach. Formulations were evaluated for floating lag time, duration of floating, dimensional stability, drug content and in vitro drug release profile. The formulations were found to have floating lag time less than 1min. Drug releases

were slow from formulations F2, F3 and F5 and the release of drug from them were found to be 80.66% ± 1.96%, 79.11%± 2.322% and 87.16% ± 2.377% respectively.

32) **Shalini Gupta *et al.,*** [44] formulated Rosuvastatin Calcium tablets using sodium starch glycolate as super-disintegrant and Dibasic-Calcium Phosphate used as stabilizing agent. Tablets were evaluated by different parameters such as thickness, hardness, friability, weight variation, In-vitro dissolution studies, content of active ingredient, stability studies and FT-IR studies .The evaluated property of the finished product complies with the In-house specification. In vitro release from the formulation was studied as USP dissolution procedure. The formulation gave an immediate release effect. The Stability Study of optimized batch was carried out for one month as per ICH guidelines and no changes were found. They were concluded that tablet of Rosuvastatin 10 mg suited for therapy anti-hyper-lipidemic.

33) **Vidyadhara S *et al.,*** [45] made an attempt to enhance the solubility, dissolution rate and oral bioavailability of poorly soluble rosuvastatin by formulating rosuvastatin calcium as solid dispersions using various techniques with polyethylene glycol (PEG) 6000 as a carrier. Fast dissolving tablets of rosuvastatin were prepared with super disintegrants like sodium starch glycolate, Croscarmalose sodium, pregelatinized starch and mannitol from the optimized solid dispersions. Tablets were evaluated for physical parameters and drug release by in vitro dissolution studies. Surface characteristics, drug-excipient interactions and crystal morphology of optimized solid dispersions were evaluated by SEM analysis, DSC and XRD studies, respectively.

34) **KPR Chowdary *et al.,*** [46] prepared and evaluated solid dispersions of aceclofenac in combined carriers, a water dispersible new modified starch namely starch phosphate and a water soluble surfactant namely Gelucire 50/13 for enhancing the dissolution rate and dissolution efficiency of aceclofenac in a 2^2 factorial study.

PATENTS IN FDDS:

Table: Patents on floating drug delivery systems.

S.No	Type of formulation	Patent number
1	Gastro retentive dosage form	U.S- 7413752
2	Multiple unit floating dosage form	EP- 10697
3	Bilayer floating tablet	EP-002445
4	Floating tablet	U.S-6635279
5	Floating microspheres	U.S-6207197
6	3- Layer floating tablets	U.S-5780057
7	Floating device	U.S-4055178
8	Floating capsule	U.S-4126672
9	Empty globular shells	U.S-3976164
10	Floating granules	U.S-4844905

AIM AND PLAN OF WORK

AIM AND PLAN OF WORK

THREE MAIN CONCEPTS

- Sustaining the action of Propranolol hydrochloride by gastroretentive (Regio-selective) floating technology to avoid repeated dosing.
- Improvement of solubility of poorly soluble Rosuvastatin calcium, BCS Class II drug by solid dispersion technique.
- Regio-selective floating bilayer tablet technology for combined administration of both the drug.

AIM OF PROJECT WORK

A. The main objective of the present study is to develop Regio-selective bilayer floating tablets containing propranolol hydrochloride as sustained release layer and Rosuvastatin calcium as immediate release layer for coronary heart disease related events.
B. Hypertension and hypercholesterolemia are the two leading risk factors for heart disease; these two together cause an increase in coronary heart disease related events.
C. To provide an effective, safe and stable pharmaceutical oral formulation containing both immediate release and sustained release of two drugs with different mechanism of action β blockers and HMG Co-A Reductase inhibitor were used. Nowadays β blockers are the most extensively used class of agents in the treatment of congestive heart failure (CHF). The HMG Co-A Reductase inhibitor have been widely used as anti hyperlipidemic drug.
D. Improvement of solubility of poorly soluble drug Rosuvastatin calcium by solid dispersion with starch phosphate.
E. To prepare Propranolol Hydrochloride SR Layer to avoid repeated dosing and to investigate the effect of the polymer and the polymer concentration on drug release.

PLAN OF WORK

- Preformulation studies.
- Raw material analysis

- Physical and chemical compatibility studies

❖ Construction of Calibration curve.

❖ Precompression studies of drug and blends.

- Bulk density
- Tapped density
- Angle of repose
- Carr's index
- Hausner's ratio

❖ Preparation of Starch phosphate.

❖ Formulation of Starch phosphate Solid dispersion

❖ FTIR spectroscopic study of solid dispersion

❖ Formulation of immediate release (IR) Solid dispersion compressed tablets.

❖ Determination of drug content of Rosuvastatin solid dispersion

❖ Physical compatibility and FTIR chemical compatibility studies

❖ Dissolution studies of Rosuvastatin solid dispersion

❖ Post compression studies of IR tablets for physical parameters like

- Physical appearance
- uniformity of weight
- hardness, thickness, diameter
- friability
- determination of drug content of IR tablets
- Disintegration studies of IR tablets.
- *Invitro* dissolution studies of IR tablets.

❖ Formulation of sustained release granules.

❖ Post compression studies of SR tablets for physical parameters like

- Physical appearance
- Hardness, Thickness, Diameter and Friability
- Determination of drug content of SR tablets
- Uniformity of weight

- Evaluation of floating characteristics of SR tablets- Buoyancy test.
- *Invitro* dissolution studies of SR tablets.

❖ Formulation of bilayer floating tablets (BFT).

❖ Post compression studies of bilayer floating tablets like

- Determination of drug content
- Uniformity of weight
- Hardness, thickness, diameter and friability

❖ Evaluation of floating characteristics of bilayer floating tablets

❖ Evaluation of release kinetics of BFT

❖ Stability studies of prepared tablets as per ICH guideline.

RATIONAL OF STUDY

RATIONALE OF STUDY

Rationale of selection of Propranolol hydrochloride as SR Floating layer[47]:

- Propranolol, a non-selective beta adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders.
- It is highly lipophilic and is almost completely absorbed after oral administration. However, much of the drug is metabolized by the liver during its first passage through the portal circulation.
- On an average, only about 25% reaches the systemic circulation. Its elimination half-life is also relatively short (about 2–6 h).
- It shows pH dependent solubility; solubility at pH 1.2 is 225 mg/ml, while at pH 6.8 it is 130mg/ml. In addition, the drug is stable at acidic pH only; decomposes rapidly when alkaline. Solutions are most stable at pH 1.2; in aqueous solutions, propranolol decomposes with oxidation of the isopropylamine side-chain.
- A conventional tablet of propranolol hydrochloride contains a dose of 20 to 40 mg and used 3 to 4 times a day in the management of several cardiovascular disorders such as hypertension, angina pectoris and arrhythmias. Such frequent drug administration may reduce patient's compliance and therapeutic efficacy.
- The present study is to formulate floating tablet containing Propranolol hydrochloride in the SR layer to increase bioavailability and to avoid repeated dosing.

Rationale of selection of Rosuvastatin calcium as immediate release SD layer [48, 49, 50,52]:

- Rosuvastatin, as rosuvastatin calcium is a HMG-CoA reductase inhibitor used for the treatment of dyslipidaemia with absolute bioavailability of 20%, it is about 88% bound to plasma proteins.
- Rosuvastatin calcium belongs to BCS CLASS II drug which is water insoluble or poorly soluble and shows poor bioavailability.
- In order to increase its solubility, solid dispersion of the drug is prepared.
- Rosuvastatin (10–40 mg) monotherapy decreased LDL-C by 53% and raised HDL-C by 7%
- One of the first studies establishing clinical efficacy and superiority of rosuvastatin over other commonly used statin agents was the Statin Therapies for Elevated Lipid Levels Compared across Doses to Rosuvastatin (STELLAR) study.
- Across the range of doses, rosuvastatin reduced LDL-C by 8.2% more than atorvastatin, 26% more than pravastatin, and 12%–18% more than simvastatin ($p < 0.001$). Milligram-equivalent LDL-C reduction was greater with rosuvastatin than all other statins ($p < 0.002$). Rosuvastatin also reduced TC more significantly than all other statins ($p < 0.001$) and decreased TG more significantly ($p < 0.001$) than simvastatin and pravastatin. Similarly, rosuvastatin increased HDL-C by a mean of 7.7%–9.6% compared to 2.1%–6.8% in all other groups.

Rationale of selection of propranolol hydrochloride and rosuvastatin calcium for Regio-selective bilayer floating tablet[52]

- Beta-blockers and statins are individually associated with reduced mortality in patients undergoing noncardiac, nonvascular surgery.
- Study provides evidence that β-blockers and statins are associated with a reduction of perioperative mortality in patients undergoing noncardiac, nonvascular surgery.
- Hypertension and dyslipidemia are conditions that can coexist frequently. National Health and Nutrition Examination Survey (NHANES III) has shown that 64% of patients with hypertension also have dyslipidemia and conversely, approximately 47% of patients with dyslipidemia have hypertension. Hypertension and hypercholesterolemia are the two leading risk factors for heart disease; these two together cause an increase in coronary heart disease related events.
- Hence regio selective floating bilayer tablets of propranolol hydrochloride as sustained release layer and rosuvastatin calcium as solid dispersion compressed immediate release layer was formulated to reduce the repeated dosing frequency of propranolol hydrochloride, improved solubility of rosuvastatin calcium and improve the patient compliance.
- Thus regio-selective bilayer floating tablets of propranolol hydrochloride and rosuvastatin calcium was more beneficial for hypertensive patients

DISEASE PROFILE

DISEASE PROFILE

HYPERTENSION[53, 54, 55]:

Hypertension is defined as the condition in which the arteries have persistently elevated blood pressure. Arteries are the blood vessels that carry oxygenated blood from the heart to the blood tissues.

EPIDEMIOLOGY

Hypertension is one of the leading causes of the global burden of disease. Approximately 7.6 million deaths (13–15% of the total) and 92 million disability-adjusted life years worldwide were attributable to high blood pressure in 2001. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease.

It often is associated with additional cardiovascular disease risk factors, and the risk of cardiovascular disease increases with the total burden of risk factors. Although antihypertensive therapy clearly reduces the risks of cardiovascular and renal disease, large segments of the hypertensive population are either untreated or inadequately treated.

Both environmental and genetic factors may contribute to regional and racial variations in blood pressure and hypertension prevalence. Studies of societies undergoing "acculturation" and studies of migrants from a less to a more urbanized setting indicate a profound environmental contribution to blood pressure. Obesity and weight gain are strong, independent risk factors for hypertension.

It has been estimated that 60% of hypertensives are >20% overweight. Among populations, hypertension prevalence is related to dietary NaCl intake, and the age-related increase in blood pressure may be augmented by a high NaCl intake. Low dietary intakes of calcium and potassium also may contribute to the risk of hypertension. Alcohol

consumption, psychosocial stress, and low levels of physical activity also may contribute to hypertension.

Criteria for diagnosis

Category	**Systolic (mmHg)**	**Diastolic (mmHg)**
Optimal blood pressure	<120	<80
Normal blood pressure	<130	<85
High normal blood pressure	130-139	85-89
Hypertension stage 1(mild)	140-149	90-99
Hypertension stage 2(moderate)	160-179	100-109
Hypertension stage 3(severe)	≥180	≥110

CLASSIFICATION:

Primary hypertension

It is also called essential or idiopathic hypertension, affects 90-95% of hypertensive individuals. The causes include genetic and environmental factors.

Secondary hypertension

It is caused by another medical condition or treatment. Their cause includes kidney problems, adrenal gland tumors, thyroid disease and narrowing of aorta.

RISK FACTORS:

FOR PRIMARY HYPERTENSION:

- Family history
- High intake of sodium and fat
- Sedentary life style
- Obesity, stress

- Excessive alcohol consumption

FOR SECONDARYHYPERTENSION:

- Renal Artery disease
- Mineral deficiencies(calcium, potassium, magnesium)
- Brain tumour , quadriplegia, head injury
- Thyroid, pituitary or parathyroid dysfunction.

PATHOPHYSIOLOGY:

The exact cause of hypertension is unknown. Arterial Blood Pressure is a product of cardiac output and peripheral resistance. Peripheral resistance is increased by factors that increase blood viscosity or reduce the lumen size of vessels.

Mechanisms leading to hypertension are

- Changes in the arteriolar blood causing increased peripheral vascular resistance.
- Increased blood volume resulting from renal or hormonal dysfunction.
- Arteriolar thickening caused by genetic factors leading to increased peripheral resistance.
- The rennin angiotensin aldosterone system along with abnormalities in renal tubules also plays a part.
- Increased circulatory blood volume and increased peripheral
- Resistance is main pathophysiological mechanisms.

SIGNS AND SYMPTOMS:

- Headache, some quite severe
- Dizziness
- Fatigue
- Irregular heart beat
- Confusion

- Vision problems
- Chest pain
- Nocturia

DIAGNOSIS:

- Blood pressure measurements show elevation.

Blood chemistry reveals elevated blood urea nitrogen and serum.

- Creatinine levels suggestive of renal disease or hypokalaemia indicating adrenal dysfunction.
- Chest X-ray shows cardiomegaly.
- Urine analysis shows protein, casts, red blood cells, white blood cells suggesting renal disease.
- Electrocardiography detects left ventricular hypertrophy or ischemia.
- Echocardiography reveals left ventricular hypertrophy.

TREATMENT:

Lifestyle modification to reduce risk factors

- Diuretics
- Angiotensin converting enzymes (ACE)inhibitors
- Alpha adrenergic receptor blockers
- Beta adrenergic receptor blockers
- Calcium channel blockers
- Central adrenergic inhibitors
- Vasodilators

DYSLIPIDEMIA [56, 57]:

DEFINITION:

Dyslipidemia is an abnormal amount of lipids (cholesterol and / or fat) in the blood. In developed countries, most dyslipidemias are hyperlipidemias; that is an elevation of lipids in the blood. This is often due to diet and lifestyle. Prolonged elevation of insulin levels can also lead to dyslipidemia. Likewise, increased levels of O-GlcNAc transferase (OGT) may cause dyslipidemia.

	Increase	Decrease
LIPID	❖ Hyperlipidemia : - Hypercholesterolemia: due to defect of chromosome 19. - Hyperglyceridemia: glycerides. - Hypertriglyceridemia: triglycerides	❖ Hypolipidemia ❖ hypercholesterolemia
LIPOPROTEIN	❖ hyperlipoproteinemia: lipoprotein (usually LDL) ❖ hyperchylomicronemia chylomicrons	❖ hypolipoproteinemia: lipoprotein ❖ abetalipoproteinemia: β-lipoprotein ❖ tangier disease: HDL
BOTH	Combined hyperlipidemia: both LDL and triglycerides	

HYPERLIPIDEAMIA

The lipids of human plasma are transported in macromolecular complexes termed lipoproteins. A number of metabolic disorders that involve elevations in levels of any of the lipoprotein species are thus termed hyperlipoproteinemias or hyperlipidemias. Term hyperlipidemia denotes increased levels of triglycerides in plasma. Hyperlipidemia is a major cause of atherosclerosis and atherosclerosis- associated conditions such as coronary heart disease (CHD), ischemic cerebrovascular disease and peripheral vascular disease.

Hyperlipidemia (elevated levels of triglycerides or cholesterol) and a reduced HDL-C level occurs as a consequence of several interrelated factors that affect the

concentrations of the various plasma lipoproteins. These factors may be lifestyle or behavioral (diet or exercise), genetic (mutations in gene regulating lipoprotein levels) or metabolic (diabetes mellitus) or other conditions that influence plasma lipoprotein metabolism.

Lipoprotein transport in the blood

Lipids and cholesterol are transported through the blood as macromolecular complexes of lipid and protein known as lipoproteins. These consist of a central core of hydrophobic lipid (triglycerides and cholestryl esters) encased in a more hydrophilic coat of polar substances- phospholipids, free cholesterol and associated apolipoproteins. There are four main classes of lipoproteins differing in relative proportion of the core lipids and in the type of apoprotein. They differ on the basis of their size and density.

They are classified into:

1. High density lipoproteins (HDL)
2. Low density lipoproteins (LDL)
3. Very Low density lipoproteins (VLDL)
4. Chylomicrons

Each of this lipoprotein classes has a specific role in lipid transport in the circulation and there are different pathways for exogenous and endogenous lipids. In the exogenous pathway cholesterol and triglycerides are absorbed from the gastrointestinal tract and transported in the lymph and then in the plasma as chylomicrons (diameter 100-1000nm) to muscle and adipose tissue. Here the cores of chylomicrons are hydrolyzed by lipoprotein lipase and the tissues take up the resulting free fatty acids.

The chylomicron remnants (30-50nm), still containing their full complement of cholestryl esters pass to the liver, bind to the receptors on hepatocytes and undergo endocytosis. Cholesterol is liberated within the liver cell and may be stored, oxidized to bile acids or secreted in the bile unaltered. Alternatively, it may enter the endogenous pathway of lipid transport in VLDL.

In the endogenous pathway cholesterol and newly synthesized triglycerides are transported from the liver as VLDL (30-80nm) to muscle and adipose tissues where the triglycerides are hydrolyzed and the resulting fatty acids enter the tissues. During this process the lipoprotein particles become smaller (20-30nm) but still have a full complement of cholestryl esters and ultimately become LDL, which provides the source of cholesterol for incorporation into cell membranes and for synthesis of steroids and bile acid.

ETIOLOGY:

Primary and secondary causes contribute to dyslipidemia.

PRIMARY CAUSES:

Primary causes are single and multiple gene mutations that result in either overproduction or defective clearance of TG and LDL cholesterol or in underproduction or excessive clearance of HDL.

SECONDARY CAUSES:

Secondary causes contribute to most cases of dyslipidemia in adults. The most important secondary cause in developed countries is a sedentary lifestyle with excessive dietary intake of saturated fat, cholesterol and transfats.

Diabetes is an especially significant secondary cause because patients tend to have an atherogenic combination of high TGs; high small, dense LDL fractions; and low HDL (diabetic dyslipidemia). Patients with type 2 diabetes are especially at risk.

SIGNS AND SYMPTOMS:

- Dyslipidemia itself usually causes no symptoms but can lead to symptomatic vascular diseases including coronary artery disease (CAD) and peripheral arterial disease.
- High levels of TGs (>1000mg/dL) can cause acute pancreatitis.

- High levels of LDL can cause eyelid xanthelasmas; arcuscorneae; and tendinous xanthomas at the Achilles, elbow and knee tendons and over metacarpophalangeal joints.
- Severe hypertriglyceridemia (>2000mg/dL) can give retinal arteries a creamy white appearance (lipemiaretinalis).
- Extremely high lipid levels give a lactescent (milky) appearance to plasma.
- Symptoms include Parasthesias, Dyspnea and Confusion.

DIAGNOSIS:

- Diagnosis is by measuring plasma levels of total cholesterol, TGs and individual lipoproteins.
- LDL cholesterol values are more often calculated as the amount not contained in HDL and VLDL. VLDL is estimated by TG ÷ 5 because the cholesterol concentration in VLDL particles is usually 1/5 of the total lipid in the particles.
- Thus LDL Cholesterol= TC-[HDL C+ (TG ÷ 5)].

Classification of plasma lipid levels

Total cholesterol

<200mg/dl	Desirable
200-239mg/dl	Borderline high
>240mg/dl	High

High density lipoprotein- Cholesterol

<40mg/dl	Low
>60mg/dl	High

Low density lipoprotein- Cholesterol

<100mg/dl	Optimal
100-129mg/dl	Near optimal
130-159mg/dl	Borderline high
160-189mg/dl	High
>190mg/dl	Very high

Triglycerides

<150mg/dl	Normal
200-499mg/dl	Borderline high
200-499mg/dl	High
>500mg/dl	Very high

SCREENING:

A Fasting lipid profile (TC, TG, HDL-C and LDL-C) should be obtained in all adults ≥ 20 years and should be repeated every five years.

MANAGEMENT:

The main goal of dyslipidemia management is to maintain blood cholesterol level within the normal range as possible.

- Lifestyle modification focusing on the reduction of saturated fat and cholesterol intake.
- Weight loss.
- Increased physical activity.
- Smoking cessation.

TREATMENT:

DRUGS- FOUR CLASSES OF LIPID LOWERING DRUGS ARE

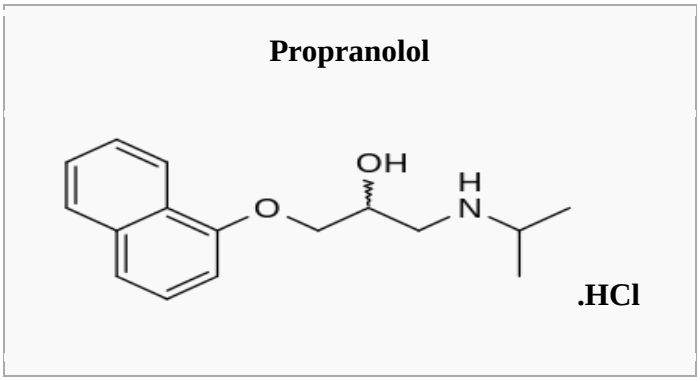
- HMG CoA reductase inhibitors (statins)
- Fibrates (gemfibrozil, clofibrate, fenofibrate).
- Niacin (nicotinic acid).
- Bile acid binding resins(colestipol, cholestyramine)

DRUG PROFILE

DRUG PROFILE

PROPRANOLOL HYDROCHLORIDE[58]

Chemical structure



Molecular formula : $C_{16}H_{21}NO_2.HCL$

Molecular weight : 259.34 g/mol

Chemical name : (RS)-1-(1-methylethylamino)-3-(1-naphthyloxy)

Propan-2-ol

Characters

Appearance : White or almost white, crystalline powder, slightly

Hygroscopic

Solubility : Freely soluble in water, sparingly soluble in alcohol

Loss on drying : 0.2634%

Melting point : 165.5^0C

Sulphated ash : 0.0224%

Pharmacokinetics[59]

- Absorption : Propranolol is almost completely absorbed from the GI tract; however, plasma concentrations attained are quite variable among individuals. Rapidly absorbed, peak plasma concentration within 2 hours (conventional tablet); 5hours (modified release)
- Protein binding : More than 90%
- Metabolism : Propranolol is extensively metabolized with most metabolites appearing in the urine
- Half-life : 4 hours
- Excretion : Via urine mainly as metabolites.

Mechanism of action

- Propranolol competes with sympathomimetic neurotransmitters such as catecholamine for binding at beta β (1)-adrenergic receptors in the heart, inhibiting sympathetic stimulation.
- This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension.

Adverse reactions

Symptoms of overdose include bradycardia, cardiac failure, hypotension, and bronchospasm. LD_{50}=565 mg/kg (orally in mice).

Dosage : Oral- 10 mg BD to 160 mg QID thrice daily.

i.v - 2 to 5 mg injected over 10 mins with constant

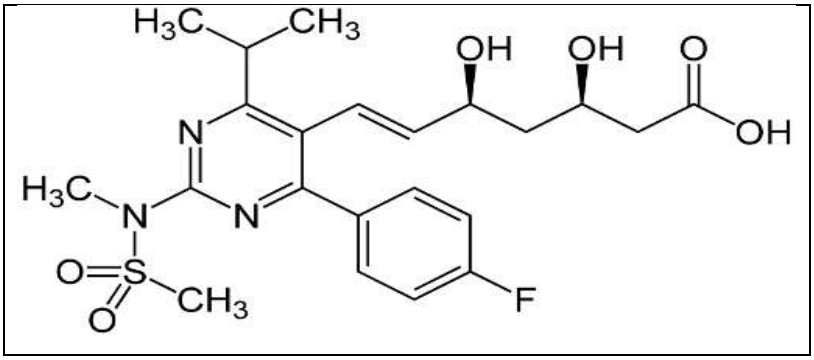
Monitoring

Contra indications : Contraindicated in pregnancy, lactation, hypersensitivity.

Administration	: Taken with food
Therapeutic indications	: Anti-anxiety, Antihypertensive and Adrenergic β -Antagonists, Adrenergic drug Vasodilator

Rosuvastatin calcium[58,60]

Chemical structure



Molecular formula : $(C_{22}H_{27}FN_3O_6S)_{2Ca}$

Molecular weight : 1001.14 g/mol

Chemical name :(bis[(E)-7-[4(-flurophenyl)-6-isopropyl-2[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,4S)-3,5-dihydroxyhept-6-enoic acid] calcium salt

Characters

Appearance : An Off White to creamish white crystalline powder

Solubility : Sparingly soluble water and methanol and slightly Soluble in ethanol

Loss on drying : ≤ 5%

Melting point : 122^0C

Sulphated ash : ≤0.1%

Pharmacokinetics[61]

- Absorption : Rosuvastatin calcium reaches the peak plasma concentration within 3 to 5 hours following the oral dosing. The absolute bioavailability is approximately 20%.
- Protein binding : More than 88% bound to plasma protein, mostly albumin
- Metabolism : Rosuvastatin calcium is not extensively metabolized. About 10% is available as its metabolite most metabolites appearing in the urine
- Half-life : 19 hours
- Excretion : Following oral administration it is primarily excreted in the faeces (90%). About 28% excreted via urine and 72% by hepatic route.

Mechanism of action

- Rosuvastatin calcium is a competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Rosuvastatin acts primarily in the liver and results in the decrease in plasma LDL and VLDL.

Adverse reactions

It is generally well tolerated. Side effects include myalgia, constipation, asthenia, abdominal pain and nausea. Other possible side effects include myotoxicity (myopathy, myositis and rhabdomyolysis) and hepatotoxicity

Dosage : Oral- 10 mg to 40 mg per day (film coated tablets)

Contra indications : hypersensitivity Patients with active liver disease,

Administration : Taken with or without food

Therapeutic indications : As hypolipidemic agent

Conventional tablets available in the market:

Crestor® (AstraZeneca)

Rosulip® (Cipla)

Razel® (Glenmark)

Novastat® (Lupin)

Rosuvas® (Ranbaxy)

EXCIPIENT PROFILE

EXCIPIENTS PROFILE[62]

PHARMACEUTICAL EXCIPIENTS:

Excipients are substances other than the pharmacologically active drug or prodrugs, which are included in the manufacturing Process or contained in the pharmaceutical finished product or dosage Form.

Excipients play a wide variety of functional role in pharmaceuticals dosage forms including,

- Modifies the solubility and bioavailability of active pharmaceutical ingredients (APIs).
- Increasing the stability of active ingredients the dosage forms.
- Maintaining the pH and/or osmolarity of liquid formulations.
- Helping active ingredients maintained preferred polymorphic Forms or conformation
- Modulating immunogenic responses of active ingredients (e.g., adjuvants).
- Acting as

    - Antioxidants
    - Emulsifying agents
    - Aerosol propellant
    - Tablet binders
    - Tablet disintegrant.

HYDROXY PROPYL METHYL CELLULOSE[62]

1. **Non-proprietary Name:**

   BP: Hypromellose, JP: Hypromellose PhEur: Hypromellose USP: Hypromellose

2. **Synonyms:**

   Benecel MHPC; E464; hydroxyl propyl methyl cellulose ;HPMC hypromellosum; methocel; methyl cellulose propylene glycol ether; methyl hydroxyl propyl cellulose; metolose ; MHPC; Pharmacoat; Tylophor; Tylose

3. **Chemical Name:**

   Cellulose hydroxyl propyl methyl ether

4. **Molecular weight:**

   Molecular weight approximately 10000-1500000

5. **Functional category**:

   Bio adhesive material, coating agent, controlled release agent, emulsifying agent, film forming agent, suspending agent, sustained release agent, tablet binder.

6. **Description:**

   Hypromellose is an odourless and tasteless, white or creamy – white fibrous or granular powder.

7. **Solubility :**

   Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%) and ether

8. **Applications:**

   HPMC is widely used in oral, ophthalmic, nasal and topical pharmaceutical formulations.it is used as tablet binder in film-coating and as a matrix for extended release tablet formulations .concentrations between 2-5% used as binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of

drugs from a matrix at levels of 10-80%w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25-5.0%

STARCH[62]

1. Non-proprietary Name:

BP: Maize starch, potato starch, tapioca starch, rice starch JP: corn

Starch, potato starch, rice starch, wheat starch pea starch, wheat starch USP NF: Cornstarch, potato starch, tapioca starch

2. **Synonyms:**

Amido; amidon ;amilo ;amylum; C*PharmGel; Eurylon; fecule; Hylon;Maydisamylum; Melojel; meritena; oryzaeamylum; pearl; perfectamyl;Pisiamylum; solaniamylum.

3. Chemical Name:

Starch

4. Empirical Formula:

$(C_6H_{10}O_5)$Where n=300-1000.

5 .Functional category:

Tablet and capsule diluents, disintegrant, binder and thickening agent.

6. Description:

Starch occurs as odorless and tasteless, white to off-white powder.

7. Solubility:

Practically insoluble in cold water (96%) and in cold water. Starch becomes soluble in hot water at temperatures above the gelatinization temperature. Starch is partially soluble in dimethylsulfoxide and dimethylformamide.

8. Applications:

Starch is a versatile excipient used primarily in oral solid- dosage formulations were it is utilized as binder, diluents, and disintegrant. In tablet formulations freshly prepared starch paste is used at a concentration of (5-10%, depending on the starch type) as a binder.

SODIUM STARCH GLYCOLATE[62]

1. Non-proprietary name:

BP: Sodium starch glycolate, phEur: sodium starch glycolate.

2. Synonyms:

Carboxymethyl starch, sodium salt, carboxymethyl amylum natricum; Explosol, glycolys, primojel, tablo; viva star p.

3. Chemical name:

Sodium carboxy methyl starch.

4. Functional category:

Tablet and capsule disintegrant.

5. Description:

Sodium starch glycolate is a white or almost white free- flowing hygroscopic powder.

6. Solubility:

Practically insoluble in methylene chloride. It gives a translucent suspension in water.

7. Applications:

It is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablet prepared by direct compression or wet granulation process. The usual concentration employed in formulation is between 2% and 8%, with the optimum concentration of about 4%.disintegration occurs by rapid uptake of

water and enormous swelling. Increasing the tablet compression pressure also appears to have no effect on disintegration time.

MAGNESIUM STEARATE[62]

1. Non-proprietary names:

BP:Magnesium stearate, JP: magnesium stearate,

PhEur:magnesium stearate, USP-NF:Magnesium stearate.

Synonyms:

Dibasic magnesium stearate, Magnesiudistearate; Magnesia stearas; magnesium octadecanoate; octadecanoicacid, magnesiumsalt; Synpro 90.

2. Chemical name:

Octa decanoic acid, Magnesium salt.

3. Empirical formula:

$C_{36}H_{70}MgO_4$

5. Molecular weight:

591.24

6. Functional category:

Tablet and capsule lubricant.

8. Description:

Magnesium stearate is a very fine, light white, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

9. Incompatibilities:

Incompatible with strong acids, alkalis and iron salts.

10. Applications:

It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0%w/w. It is hydrophobic and may retard the dissolution of a drug from solid dosage form. The lowest possible concentration is therefore used in such formulations.

ETHYL CELLULOSE[62]

1. Non-proprietary names:

BP: Ethyl cellulose, PhEur: Ethyl cellulose, USP-NF: Ethyl cellulose

2. Synonyms:

Aquacoat ECD; Aqualon; Ashacel; E462; Ethocel; Ethylcellosum; surelease.

3. Chemical name:

Cellulose ethyl ether.

4. Empirical formula & Molecular weight:

Ethyl cellulose is partially ethoxylated. Ethyl cellulose with complete ethoxyl substitution (DS=3) is $C_{12}H_{23}O_6$ $(C_{12}H_{22}O_5)_n$ $C_{12}H_{23}O_5$ where may vary to provide a wide variety of molecular weight.

5. Functional category:

Coating agent, flavoring agent; tablet binder; tablet filler viscosity increasing agent.

6. Description:

Ethyl cellulose is a tasteless, free flowing, white to light tan – colored powder.

7. Incompatibilities:

Incompatible with paraffin wax and microcrystalline wax.

8. Applications:

The main use of ethyl cellulose in oral formulation as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask the unpleasant taste or to improve the stability of a formulation; modified release tablet formulation May also be produced using ethyl cellulose as a matrix former. High viscosity grade are used in microencapsulation. It is used as a binder in dry or wet granulation process of tablets and thickening agent in creams, lotions and gels.

XANTHUM GUM[62]

1. Non-proprietary names:

BP: Xanthan gum, PhEur: Xanthani gummi, USP-NF: Xanthan gum

2. Synonyms:

Corn sugar gum; E415; Keltrol; polysaccharide B-1459, Rhodigel, Vansan NF, Xantural.

3. Chemical name:

Xanthan gum

4. Empirical formula and Molecular weight:

$(C_{35}H_{49}O_{29})_{n.}$ Xanthan gum as a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as a dominant hexose units, along with D- glucuronic acid and is prepared as the sodium, potassium or calcium salt.

5. Structural formula:

Each xanthan gum repeat units contains five sugar residues: two glucose, two mannose and one glucuronic acid. The polymer backbone consist of four b-D-glucose units linked the 1 and 4 positions and is therefore identical in structure to cellulose

6. Functional category:

Stabilizing agent; viscosity increasing agent; suspending agent.

7. Description:

Xanthan gum occurs as a cream or whit colored odorless, free flowing, fine powder

8. Applications:

Xanthan gum is widely used in oral and topical formulation cosmetics and food as a stabilizing agent. It is also used as emulsifying agent and thickening agent.it is non- toxic, compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over wide pH and temperature range.it is also used as a matrix former in sustained release tablets.it increases the retention time of the ophthalmic solutions in eye and as Bioadhesive polymer.

9. Stability:

Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3-12), the stability at pH 4- 10 and temperature at 10-60℃ is maximum.

MICROCRYSTALLINE CELLULOSE[62]

1. **Non-proprietary name:**

BP: Microcrystalline cellulose USP-NF: Microcrystalline cellulose;

NF: Microcrystalline cellulose.

2. **Synonyms:**

AvicelPH; Cellulosegel, Crystalline cellulose.

3. **Chemical Name:**

Cellulose

4. **Empirical Formula:**

$(C_6H_{10}O_5)_n$ where n = 220.

5. **Functional Category:**

Tablet and capsule diluents; Adsorbent; tablet disintegrant, suspending agent;

6. **Description:**

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

7. **Solubility:**

Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

8. **Incompatibilities:**

Microcrystalline cellulose is incompatible with strong oxidizing agents.

9. **Applications:**

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as binder/diluents, microcrystalline cellulose also has some lubricant and disintegrants properties that make it useful in tableting.

SODIUM BICARBONATE[62]

1. **Non-proprietary name:**

BP: Sodium bicarbonate, JP: Sodium bicarbonate, PhEur: Natrii hydrogeno carbonas, USP: Sodium bicarbonate

2. **Synonyms:**

Baking soda; E500; Effer –soda; monosodium carbonate; Sal de vichy; Sodium acid carbonate; sodium hydrogen carbonate.

3. **Chemical Name:**

Carbonic acid monosodium salt

4. **Empirical Formula:**

$NaHCO_3$ 84.01

5. **Functional Category:**

Alkalizing and therapeutic agent.

6. **Description:**

Sodium bicarbonate occurs as an odorless, white, crystalline powder with saline, slightly alkaline taste. The crystal structure is monoclinic prisms.

7. **Incompatibilities:**

Reacts with acids, acidic salts and alkaloid salts.

8. **Applications:**

Sodium bicarbonate is used as a source of CO_2 in the formulation or technology effervescent tablets and granules. In effervescent tablet and granules, sodium bicarbonate is usually formulated with citric acid or tartaric acid; tablets prepared with sodium bicarbonate alone since the gastric fluid is sufficient to produce the effervescences; it is also used in tablet formulations to buffer the drug molecules that are weak acids, thereby increasing the rate of dissolution and reducing gastric irritation. Recently it is used as a gas generating agent in floating systems and alginate raft systems.

ISOPROPYL ALCOHOL[62]

1. Non-proprietary name:

BP: Isopropylalcohol, PhEur: Isopropylalcohol, USP: Isopropyl alcohol.

2. Synonyms:

Dimethyl carbinol, IPA, Isopropanol, petrohol, sec-propyl alcohol

3. Chemical Name:

Propan-2-ol.

4. Empirical Formula:

C_3H_8O

5. Molecular Weight:

60.1

6. Functional category:

Disinfectant, solvent

7. Description:

It is a clear, colourless, mobile, volatile, flammable liquid with a characteristic, spirituous odour resembling that of a mixture of ethanol and acetone, it has slightly bitter taste.

8. Solubility:

Miscible with benzene, chloroform, ethanol (95%), ether, glycerin and water.

9. Incompatibilities:

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid.

POVIDONE[62]

1. Nonproprietary name:

Povidone

2. **Synonyms:**

E1201; kollidon; plasdone; poly[1-(2-oxo-1-pyrolidinyl) ethylene]; polyvidone; polyvinyl pyrrolidone; povidonum; PVP; povipharm; 1-vinyl-2-pyrolidone polymer

3. Chemical name:

1 -ethenyl-2-pyrollidone homopolymer.

4. Empirical formula:

$(C_6H_9NO)_n$

5. Molecular weight:

2500-3,000,000

6. Functional category:

Disintegrant; dissolution enhancer; suspending agent; tablet binder.

7. Description:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidone with equal to or lower than 30 are manufactured by spray drying and occurs as spheres. Povidone K90 and higher k-values manufactured drum drying and occurs as plates

8. Incompatibilities:

Incompatible with inorganic salts, natural and synthetic resins.

9. Application:

In tablets, Povidone solutions are used as binders in wet granulation processes. Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol or hydro alcoholic solutions. It is used as a solubilizer in oral and parenteral formulations.

Povidone is used as a coating agent. Povidone is additionally used as suspending; stabilizing and viscosity increasing agent in topical and oral suspensions and solutions. The solubility of poorly soluble drugs can be increased by mixing with povidone

ERYTHROSIN[63]

1. Nonproprietary name:

Erythrosine natrium

2. Synonyms:

Erythrosine B; Erythrosin B; Acid Red 51; C.I. 45430; FD & C Red No.3; E127; 2',4',5',7'-Tetraiodo-3',6'-dihydroxy-spiro[3H-isobenzofuran-1,9'-xanthen]-3-one disodium salt; Tetraiodofluorescein Sodium Salt; Calcoid Erythrosine N; 2,4,5,7-Tetraiodo-3,6-dihydroxyxanthene-9-spiro-1'-3H-isobenzofuran-3'-one disodium salt; 2',4',5',7'-Tetraiodofluorescein, disodium salt; C.I.Food Red 14; Aizen Erythrosine; Tetraiodifluorescein, disodium salt; Spiro[isobenzofuran- 1(3H),9'-[9H]xanthen]-3-one, 3',6'-dihydroxy-2',4',5',7'-tetraiodo-, disodium salt

3. Chemical name:

2-(6-Hydroxy-2, 4, 5, 7-tetraiodo-3-oxo-xanthen-9-yl) benzoic acid

4. Empirical formula:

$C_{20}H_6I_4Na_2O_5$

5. Molecular weight:

879.86 g/mol

6. Melting point:

303 °C

7. Functional category:

It is cherry-pink synthetic colorant

8.Description:

Maroon color powder and hygroscopic

9.Application:

Erythrosine B is an iodo derivative of fluorescin with distinctly bluish shade whereas eosin is a bromine derivatives of fluorescin. It is used in coloring cosmetics and food. It is used as a plasma stain for nerve cells and staining bacteria in soil. It is used as a phosphorescent triplet probe to detect rotational diffusion of membrane proteins

STARCH PHOSPHATE[64]

Solubility of starch phosphate was tested in water, aqueous buffers of pH 1.2, 4.5, and 7.4 and organic solvents such as alcohol, dichloromethane, chloroform, acetone and petroleum ether.

1. **pH**

The pH of 1% w/v slurry was measured.

2. **Melting Point**

Melting point was determined by using melting point apparatus.

3. **Viscosity**

Viscosity of 1% dispersion in water was measured using Ostwald Viscometer**.**

4. **Swelling Index**

Starch phosphate (200 mg) was added to 10 ml of water and light liquid paraffin taken in two different graduated test tubes and mixed. The dispersion in the tubes was allowed to stand for 12 h. The volumes of the sediment in the tubes were recorded. The swelling index of the material was calculated as follows.

Volume of sediment in water – Volume of sediment in light liquid paraffin

S.I (%) = × 100

Volume of sediment in light liquid paraffin

5. Test for gelling property

The gelling property (gelatinization) of the starch and starch phosphate prepared was evaluated by heating a 7% w/v dispersion of each in water at 100°C for 30 min.

6. Moisture absorption

The hygroscopic nature of starch phosphate was evaluated by moisture absorption studies in a closed desiccator at 84% relative humidity and room temperature.

7. Particle size

Particle size analysis was done by sieving using standard sieves.

8. Density

Density (g/cc) was determined by liquid displacement method using benzene as liquid.

9. Bulk density

Bulk density (g/cc) was determined by three tap method in a graduated cylinder.

10. Angle of repose

Angle of repose was measured by fixed funnel method.

11. Compressibility index

Compressibility index (CI) was determined by measuring the initial volume (Vo) and final volume (V) after hundred.

MATERIALS AND METHODS

MATERIALS AND METHODS

Table 2: List of materials and their applications in formulation

S.No	Name of material	Manufacturer / supplier	Use in formulation
1	Propranolol hydrochloride	Sri Sai supreme chemicals	Active ingredient
2	Rosuvastatin calcium	Biocon Pharma Ltd	Active ingredient
3	HPMC K4M	Pharma French Ltd	Hydrophilic polymer
4	HPMC K100M	Pharma French Ltd	Hydrophilic polymer
5	Xanthan gum	Pharma French Ltd	Hydrophilic polymer
6	Ethyl cellulose	Pharma French Ltd	Non swellable polymer
7	Micro crystalline cellulose	Pharma French Ltd	Diluent
8	Starch	Pharma French Ltd	Diluent
9	Sodium starch glycolate	Pharma French Ltd	Super disintegrant
10	Sodium bicarbonate	Indian research products	Gas generating agent
11	PVP K30	Kniss laboretories	Binding agent
12	Magnesium stearate	Kniss laboretories	Lubricant
13	Isopropyl alcohol	Microfine chemicals	Solvent
14	Erythrosine	Kwality pharmaceuticals	Colorant

Table 3: List of equipments used

S.NO	Equipment's / instruments	Manufacturer /supplier
1	Electronic weighing balance	Asha scientific company, Mumbai
2	Hot air oven	MC Dalal, Chennai
3	10 Station compression machine	Rimek, India
4	Vernier caliper	Mitutoyo, Japan
5	Monsanto hardness tester	Erweka, Mumbai
6	Friabilator	Electrolab, India
7	P^H meter	MC Dalal, Chennai
8	Disintegration apparatus	Electrolab, India
9	Dissolution tester	Veego, India
10	UV-visible spectrophotometer	Shimadzu, Japan
11	Fourier transform infra-red spectrophotometer	Nicolet, India

PREFORMULATION STUDIES

The Preformulation studies are conducted to establish the physiochemical characteristics of the drug and its compatibility with the various excipients. The Preformulation studies are necessary to formulate drug into stable, safe and effective dosage form.

Drug-excipient compatibility study

The drug and excipients selected for the formulation are evaluated for physical and chemical compatibility studies.

Physical compatibility study[67]:

The physical compatibility studies are conducted to provide valuable information to the formulator in selecting the appropriate excipients for the formulation. It was done by mixing the drugs and excipients and kept at room temperature and at 40°C and 75%RH. Any color change of the physical mixture was observed visually.

Chemical compatibility study[67]:

Pure drugs, polymers, excipients, drug-excipient mixture was subjected to FTIR to investigate the drug-excipient interactions. The IR spectra of test samples are obtained using potassium bromide pellet method.

Calibration curve :

1. Calibration curve of Propranolol Hydrochloride[65]

   100mg of Propranolol was dissolved in 10ml of 0.1 N HCl and made upto 100ml using 0.1N HCL in standard flask. From the above solution 10ml was taken and made upto 100ml using 0.1N HCL. From the above solution 2ml,4ml, 6ml,8ml and 10ml were taken and upto 100ml using 0.1N HCL. The absorbance of resulting solutions is measured at 290nm using UV spectrophotometer. Calibration curve was plotted.

2. Calibration curve of Rosuvastatin calcium[66]

   50 mg of Rosuvastatin calcium was dissolved in 5ml of Methanol and made upto 50ml using 0.1N HCL in a 50ml standard flask. From the above solution 5ml was taken and made upto 50ml using 0.1N HCL. From the above solution 2ml,4ml, 6ml,8ml and 10ml were taken and made upto 100ml using 0.1N HCL. The absorbance of resulting solutions is measured at 240nm using UV spectrophotometer. The Calibration curve was then plotted.

Precompression studies of drugs and blends

The flow property measurements include bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. The flow property measurements of drugs and blends are determined to select the type of granulation to be carried out in the formulation.

I. Bulk density[67]

   Bulk density is the ratio of weight of powder to bulk volume. A sample of 10g of powder has been carefully introduced into measuring cylinder with the aid of funnel and volume occupied by the powder was noted. Bulk density is expressed in g/ml.

$$\text{Bulk density} = \frac{M}{V_b}$$

Where,

M = weight of sample in grams

Vb=bulk volume

II. Tapped density[67]

Tapped density is the ratio of weight of powder to tapped volume of powder. The 10g of powder was introduced into the measuring cylinder with the aid of funnel and tapped for 500 times on a hard wooden surface at 2 seconds interval and the volume obtained was noted. Tapped density is expressed in g/ml

$$\text{Tapped density} = \frac{M}{Vt}$$

Where,

M = weight of sample in grams

Vt= tapped volume

III. Angle of repose[67]

Angle of repose measures the frictional force involved in the powder. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is determined by fixed funnel method. The powder mixtures allowed to flow through the funnel method to a stand at define height. The angle of repose is then calculated by the formula mentioned below.

$$\theta = \tan^{-1}(h/r)$$

Where,

θ= angle of repose in degrees

h= height of the pile of powder in cm

r= radius of pile of powder in cm

Table 4: Angle of repose

Flow property	Angle of repose (in degrees)	Compressibility index (%)	Hausner's ratio

Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>65	>38	>1.60

I. Compressibility index or Carr's index[68]

Compressibility index is the measure of flow property of a powder. It is measured for determining the relative importance of interparticulate interactions. It is expressed in percentage and calculated by formula mentioned below.

$$\text{Compressibility index} = \left(\frac{\text{Tapped density - bulk density}}{\text{Tapped density}} \right) \times 100$$

II. Hausner's ratio[68]

Hausner's ratio is the measure of propensity of powder to be compressed and also interparticulate interactions. Hausner's ratio is calculated by formula mentioned below.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

FORMULATION DEVELOPMENT[66]

Formulation of Rosuvastatin Calcium- Starch Phosphate Solid Dispersion

Preparation of Starch Phosphate

Starch phosphate was prepared based on the method of Choi et al with some modifications. Potato starch (100 g) and di-sodium hydrogen orthophosphate anhydrous (30 g) were suspended in 100 ml of water and continuously stirred for 20 min. This starch slurry was then filtered and the wet starch mixture was conditioned for 12 h at room temperature (28^0C). To enhance phosphorylation, this mixture was heated in a forced air oven at 130°C for 3 h.The product obtained was ground and sized.

Preparation of Solid Dispersions of Rosuvastatin calcium

Phosphate Solid dispersions of Rosuvastatin calcium and starch phosphate were prepared in 1:1 (SD-1), 1:2 (SD-2), 1:3 (SD-3) and 1:4 (SD-4) ratios of drug: carrier by solvent evaporation method. Rosuvastatin calcium (1 g) was dissolved in Methanol (10 ml) in a dry mortar to get a clear solution. Starch phosphate (1 g) was then added and mixed. The thick slurry was triturated for 15 min for complete evaporation of Methanol and then dried at 55^oC until dry. The dried mass was pulverized and sieved through mesh no.100.

Table 5: Formulation of Rosuvastatin solid dispersion

S.No	Ingredients	SD-1	SD-2	SD-3	SD-4
1	Rosuvastatin calcium	10	10	10	10
2	Starch Phosphate	10	20	30	40

FOR ROSUVASTATIN SOLID DISPERSION:

Fourier transforms infrared (FTIR) spectroscopy

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks. Samples were prepared in KBr disks in a hydrostatic press at 6-8 tons pressure. The scanning range was 500 to 4000 cm^{-1}

Estimation of Rosuvastatin calcium

An UV spectrophotometric method based on the measurement of absorbance at 240 nm in 0.1N HCl was used for estimation of Rosuvastatin calcium. When the standard drug solution was assayed repeatedly (n=6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.60% and 1.0% respectively. No interference from excipients used was observed.

***Invitro* dissolution study**

The *Invitro* dissolution study was carried out using a USP apparatus II in 900 ml of 0.1 N HCl for one hour for accurately weighed amount of the formulations (containing approx.10 mg of Rosuvastatin calcium). The rotational speed of the paddle was set at 50 rpm at 37 ± 0.5ºC. (10ml of solution were withdrawn at predetermined time intervals of every 10 minutes for 1h; sink conditions were maintained. The samples were analyzed for drug content using a double beam UV spectrophotometer at 240 nm

Formulation of Rosuvastatin Calcium Immediate tablets:

The immediate release tablets each containing 10 mg of Rosuvastatin calcium were prepared by wet granulation method employing Rosuvastatin calcium alone and its solid dispersions in starch phosphate. Sodium starch glycolate was used as a super disintegrant.

Starch was used as diluent to adjust the weight of the tablet to 150 mg. PVPK-30, Magnesium stearate (2%) were incorporated respectively as binder and

S.NO	INGREDIENTS	R-I	R-II	R-III

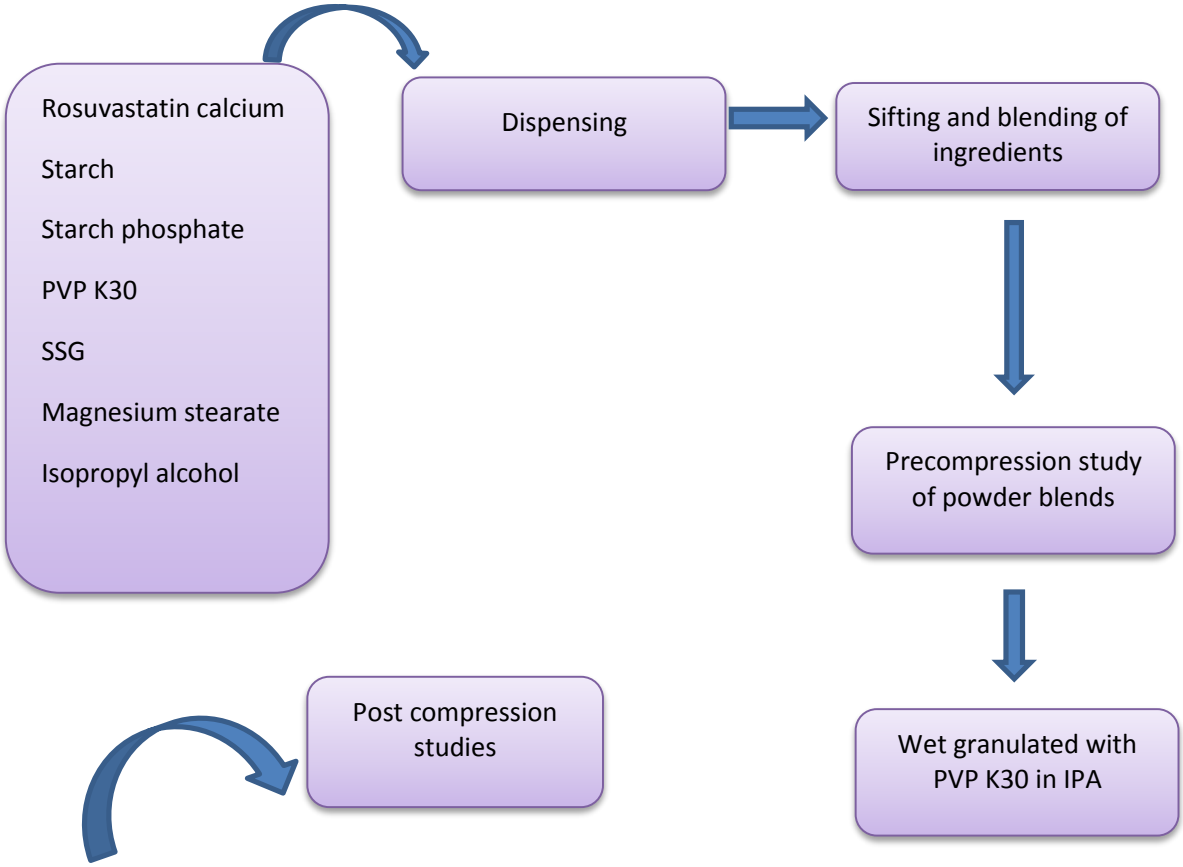
lubricants. The tablet granules were prepared by wet granulation method and then compressed into tablets on a REMEK 10-station rotary tablet punching machine using 8 mm flat punch

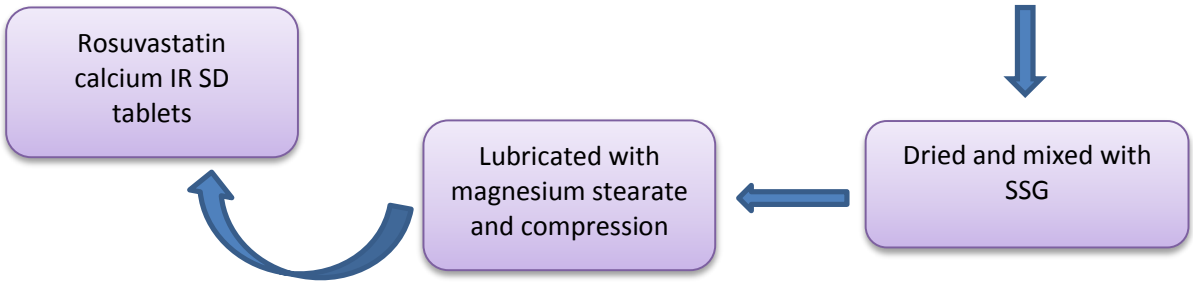
Table 6: Formulation of immediate release solid dispersion tablet of rosuvastatin calcium

1	Rosuvastatin calcium	10	-	-
2	Rosuvastatin solid dispersion	-	40	50
3	Starch	129	99	89
4	PVP K30	3	3	3
5	Sodium starch glycolate	6	6	6
6	Magnesium stearate	2	2	2
7	Isopropyl alcohol	Q.S	Q.S	Q.S

Average weight of each tablet = 150mg

The immediate release tablet of Rosuvastatin calcium was formulated and optimized. The optimized formulation was used to formulate bilayer floating tablets.





Formulation of Sustained Release Propranolol Hydrochloride floating tablets[67]

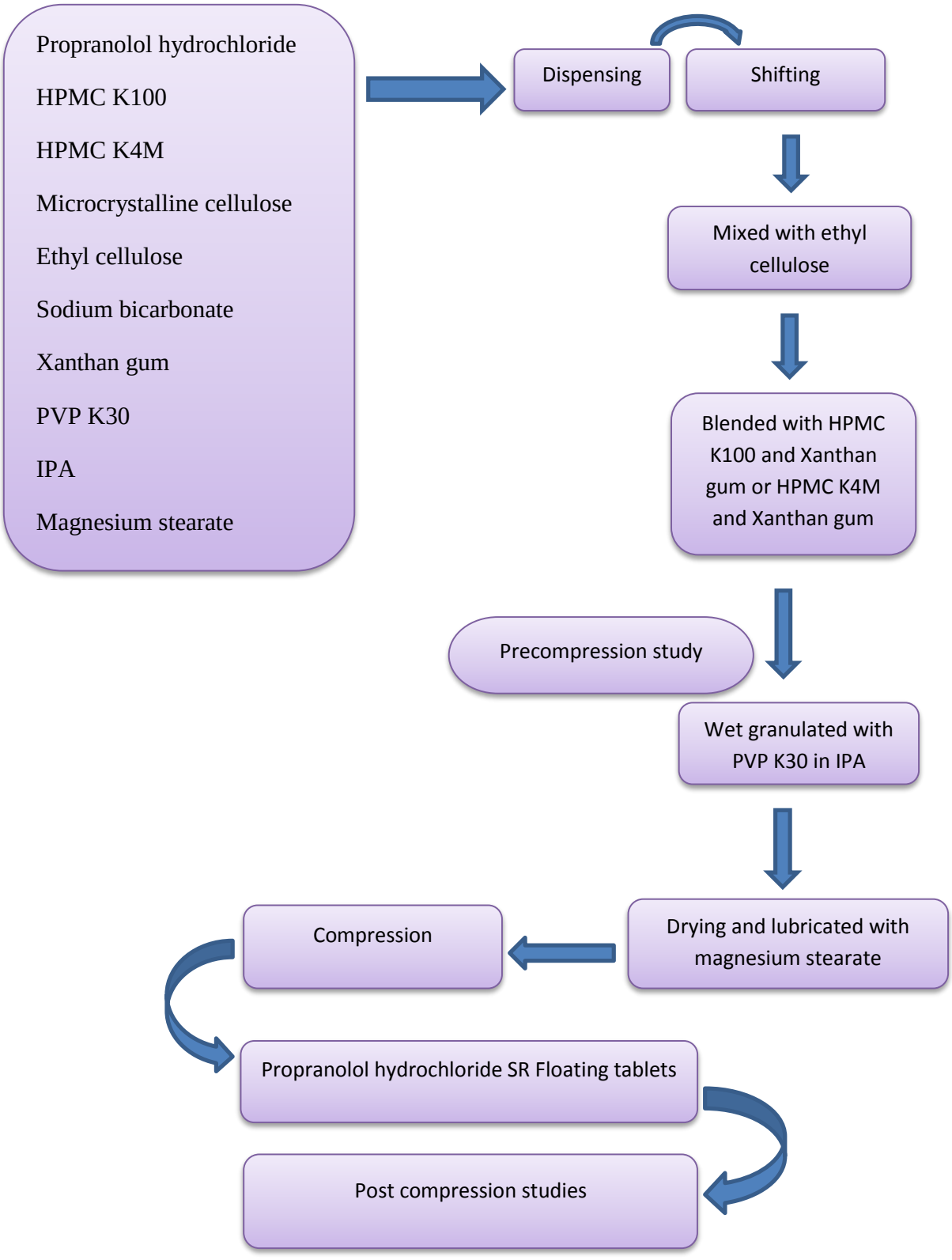
The sustained release granules of Propranolol Hydrochloride were prepared by wet granulation technique. Different polymers such as HPMC K4M, HPMC K100, Ethyl cellulose and xanthan gum were used. The concentrations of HPMC K4M and HPMC K100 were taken as variables. The granules were compressed by 10 station tablet compression machine using 8mm punches.

Table 7: Formulation of sustained release floating layer of Propranolol Hydrochloride

S.No	Ingredients	P-I	P-II	P-III	P-IV	P-V	P-VI	P-VII
1	Propranolol HCl	80	80	80	80	80	80	80

2	HPMC K 100	40	60	80	100	0	0	0
3	HPMC K4M	0	0	0	0	40	60	80
4	Xanthum gum	20	20	20	20	20	20	20
5	Microcrystalline cellulose	60.5	40.5	20.5	0.5	60.5	40.5	20.5
6	Ethyl cellulose	12.5	12.5	12.5	12.5	12.5	12.5	12.5
7	Sodium bicarbonate	20	20	20	20	20	20	20
8	PVP K 30	12.5	12.5	12.5	12.5	12.5	12.5	12.5
9	IPA	QS	QS	QS	QS	QS	QS	QS
10	Magnesium stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5

Total weight of the tablet = 250 mg


Propranolol hydrochloride
HPMC K100
HPMC K4M
Microcrystalline cellulose
Ethyl cellulose
Sodium bicarbonate
Xanthan gum
PVP K30
IPA
Magnesium stearate
Dispensing
Shifting
Mixed with ethyl cellulose
Blended with HPMC K100 and Xanthan gum or HPMC K4M and Xanthan gum
Precompression study
Wet granulated with PVP K30 in IPA
Drying and lubricated with magnesium stearate
Compression
Propranolol hydrochloride SR Floating tablets
Post compression studies

POST COMPRESSION STUDIES

1. PHYSICAL PARAMETERS

General appearance:

The general appearance of the tablets from each formulation batch was observed. The general appearance parameters are shape, color, presence or absence of odor and taste were evaluated.

Uniformity of weight[58]:

Twenty tablets were selected at a random and weighed individually. The average weight was also measured. The percentage deviation of tablets was calculated and compared with standard specifications.

Thickness and diameter[70, 71]:

The thickness and diameter was measured to determine the uniformity of size and shape. Thickness and diameter of the tablets were measured using Vernier caliper.

Hardness[71]:

Hardness is defined as the force required for breaking a tablet at diametric compression test and it is termed as tablet crushing strength. Hardness of the prepared formulations was determined using Monsanto hardness tester. It was expressed in kg/cm^2

Friability[71]:

Friability of the prepared formulations was determined by using Rochelle Friabilator. Pre-weighed sample of tablets was placed in the friability tester, which was then operated for 100 revolutions, tablets were dedusted and reweighed. The friability of the tablets was calculated using the formula mentioned below

$$\text{Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablet}}{\text{Final weight of the tablets}}$$

2. DRUG CONTENT

FOR IR TABLETS CONTAINING ROSUVASTATIN CALCIUM[48]

Twenty tablets were selected randomly and ground. The powder equivalent of 10 mg Rosuvastatin calcium was weighed, mixed with methanol and made upto 10 ml. It was kept overnight, filtered and diluted to 50 ml with 0.1N HCl acid. The standard solution was also prepared in the same manner. The absorbance of the standard and

sample solution was measured at 240 nm. The amount of rosuvastatin calcium was determined.

BILAYER FLOATING TABLETS CONTAINING PROPRANOLOL HYDROCHLORIDE AND ROSUVASTATIN CALCIUM BY SIMULTANEOUS ESTIMATION METHOD[72]

Simultaneous estimation of propranolol hydrochloride and rosuvastatin calcium was carried out using UV spectrophotometer.

PROCEDURE:

The following equations were used to determine the contents.

$$C_X = \frac{A_2 a_{y1} - A_1 a_{y2}}{a_{x2}\, a_{y1} - a_{x1}\, a_{y2}}$$

$$C_Y = \frac{A_1 a_{X2} - A_2 a_{X1}}{a_{x2}\, a_{y1} - a_{x1}\, a_{y2}}$$

Where ax_1 and ax_2= the absorptivity of drug X at λ_1 and λ_2 respectively

ay_1 and ay_2= the absorptivity of drug Y at λ_1 and λ_2 respecively

A1 and A2 = the absorbance of sample at λ_1 and λ_2 respectively

The ratios should lie outside the range of 0.1-2.0 for the precise determination of X and Y drugs respectively. This criteria is satisfied only when the λ max of the two components is reasonably dissimilar and the two components should not interact chemically.

Preparation of standard stock solution of Propranolol Hydrochloride:

Propranolol hydrochloride equivalent to 80 mg of propranolol was accurately weighed; 90 ml of 0.1N HCl was added and sonicated to dissolve. The volume was made upto the 100 ml with 0.1N HCl.

Preparation of standard stock solution of Rosuvastatin Calcium:

Rosuvastatin calcium equivalent to 10 mg of Rosuvastatin was accurately weighed; 10 ml of methanol was added and further diluted to 50 ml with 0.1N HCl.

Preparation of Mixed standard solution of Propranolol Hydrochloride and Rosuvastatin calcium

2ml each of the stock solutions of propranolol hydrochloride and rosuvastatin calcium were mixed and the volume was made upto 100ml with 0.1N HCl.

Preparation of sample solution

Twenty tablets were accurately weighed and the average weight was calculated. The tablets were then ground to a fine powder. The powder equivalent to the average weight of the tablets was mixed with 0.1N HCl and made upto100 ml. the solution was kept overnight and filtered. 10 ml of the above solution was diluted to 100ml with 0.1N HCl. The absorbance of the solution was recorded at 240 nm and 290 nm. The amount of propranolol and rosuvastatin were determined

3. *In vitro* disintegration studies for IR tablets[58]:

One tablet each was placed in each of the six tubes of the basket. The assembly was suspended in water maintained at a temperature of 37^0c ± 0.2^0c and the apparatus was operated. The time taken to disintegrate the tablets completely was noted.

4. *In vitro* floating studies for BF tablets[39]:

Floating characteristics of the prepared formulations were determined using USP paddle apparatus at a speed of 50 rpm in 900ml of 0.1N HCl solution (pH=1.2) at 37 ± 0.2^0c for 12 hours. The time between the introduction of tablet and its buoyancy on the simulated gastric fluid (floating lag time) and the time during which the dosage form remain buoyant (floating duration) were measured. Also, the matrix integrity of the tablets during the study was visually monitored.

5. *Invitro* dissolution studies:

For IR tablets[40]:

The *invitro* dissolution study of Rosuvastatin calcium was carried out using USP Type II (Paddle) dissolution apparatus under sink condition. The dissolution medium was 900 ml of a 0.1N HCl solution (pH=1.2), at 37^0c$\pm0.2^0$c at speed was 50 rpm. The in vitro release studies were carried out for 30 min by taking sample at every 5 minutes intervals. The absorbance of the solution was recorded at 240 nm using UV spectrophotometer.

For bilayer floating tablets[73]:

The *invitro* dissolution study of Propranolol hydrochloride and Rosuvastatin calcium bilayer floating tablets were determined using USP Type II (Paddle) dissolution apparatus under sink condition. The dissolution medium was 900 ml of a 0.1N HCl solution (pH=1.2), at 37^0C$\pm0.2^0$C at speed was 50 rpm. 10ml of the solution was collected from the dissolution medium at 10, 20, 30 min and at 1,2,3,4,5,6,7,8,9,10,11,12 hour and were replaced with fresh dissolution medium. The solutions were filtered through whatmann filter paper no. 41. The absorbance of the solution was recorded at 240nm and 290 nm using UV spectrophotometer.

6. Swelling studies of bilayer floating tablets[39]:

The extent of swelling was measured in terms of percentage weight gain by tablets. The swelling behavior of the optimized formulation was studied. Swelling index of the

optimized formulation was determined in 900 ml of 0.1N HCl solution (pH=1.2), at 37^0-C±0.5^0C. At the end of 1,2,3,4,5,6,7,8,9,10,11 and 12 hours. Tablets were withdrawn and the excess of fluid was removed with a tissue paper, the tablets were weighed and the percentage weight gain by the tablet was calculated using the formula.

$$SI = \frac{Mt - M_0 \times 100}{M_0}$$

Where, SI= Swelling index

Mt= Weight of tablet at time t and

M_0= Weight of tablet at time 0

7. Evaluation of *invitro* release kinetics[74]:

To study the *invitro* release kinetics of the optimized BFT, data obtained from dissolution study were plotted in various kinetics models.

1. **Zero order equation :**

The zero order release can be obtained by plotting cumulative % percentage drug released vs. time in hours. It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$C = K_0 t$$

Where K_0= Zero order constant

T= Time in hours

2. **First order equation:**

A graph was plotted with log % cumulative drug remaining Vs time in hours.

$$\text{Log } C = \log C_0 - Kt/2.303$$

Where C_0= Initial concentration of drug

K= First order

T= Time in hours

3. **Higuchi kinetics:**

A graph was plotted with % cumulative drug released vs. square root of time

$$\mathbf{Q = Kt^{½}}$$

Where K= constant reflecting design variable system (differential rate constant) t= Time in hours

4. **Hixon and Crowell erosion equation:**

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixon and Crowell rate equation. A graph was plotted with cube root of % drug remaining vs. time in hours.

$$\mathbf{Q_0^{1/3} - Qt^{1/3} = K_{HC}Xt}$$

Where Q_t= amount of drug released in time t.

Q_0= Initial Amount of drug

K_{HC}= Rate constant for Hixon Crowell equation.

5. Korsmeyer-Peppas equation:

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released vs. log time

$$\mathbf{M_t/M_\alpha = Kt^n}$$

Where Mt/M_α = fraction of drug released at time t

t= release time

K= Kinetics constant (incorporating structural and geometric characteristics of preparation)

N= Diffusional exponent indicative of mechanism of drug release

If slope (n) values is 0.5 or less, the release mechanism is fickian diffusion and if $0 < n < 1$ it follows non fickian model (anomalous model). The drug release follows zero order drug release and non fickian case – II transport if the value is 1. For the values of n higher than 1, the mechanism of drug released is regarded as non- fickian super case II transport. The model is used to analyze the drug release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release is involved.

6. Stability study[69]:

Stability study of optimized bilayer floating tablets was carried out according to ICH guidelines. All tablets were packed in blister and kept in humidity chamber at 40 ± 2^0-C and 75± 5% RH for 3 months. Samples were withdrawn at monthly intervals and analyzed for drug content, floating characteristics, hardness and *in vitro* dissolution.

RESULTS AND DISCUSSION

RESULT AND DISCUSSION

The present investigation was to formulate bilayer floating tablets for immediate release of rosuvastatin calcium and sustained release of propranolol hydrochloride for Hypertension with Hyperlipidemia.

PREFORMULATION STUDIES:

DRUG-EXCIPIENT COMPATIBILITY STUDY:

The drug-excipient compatibility study was conducted to reveal the excipient compatibility with the drug.

Table 8: Physical compatibility study of Drug and Excipients

S.No	Drug + Excipient	Description and Condition			
		Initial	Room temperature and 40^0C/ 75% RH in days		
			10^{th}	20^{th}	30^{th}
1	PH	White, almost white crystalline powder	NC	NC	NC
2	RC	White, almost white crystalline powder, Slightly Hygroscopic	NC	NC	NC
3	PH+RC	White, almost white crystalline powder	NC	NC	NC
4	HPMC K4M	White or creamy white crystalline powder	NC	NC	NC
5	HPMC K 100	White or creamy white crystalline powder	NC	NC	NC
6	Xanthan gum	Creamy white Free flowing fine powder	NC	NC	NC
7	EC	Free flowing white colored powder	NC	NC	NC
8	MCC	White, crystalline powder	NC	NC	NC
9	PVPK30	White or Creamy white colored Hygroscopic powder	NC	NC	NC
10	Sodium bicarbonate	White, crystalline powder	NC	NC	NC

11	Starch	White or off white crystalline powder	NC	NC	NC
12	Starch Phosphate	White or off white crystalline powder	NC	NC	NC
13	Magnesium Stearate	White or off white crystalline powder	NC	NC	NC
14	Erythrosine	Cherry pink color powder	NC	NC	NC
15	PH+HPMC K4M	White, creamy white crystalline powder	NC	NC	NC
16	PH + HPMCK100	White, creamy white crystalline powder	NC	NC	NC
17	PH + Xanthan gum	White, creamy white crystalline powder	NC	NC	NC
18	PH + EC	White, almost white crystalline powder	NC	NC	NC
19	PH + MCC	White, almost white crystalline powder	NC	NC	NC
20	PH + PVPK30	White, almost white crystalline powder	NC	NC	NC
21	PH + Sodium bicarbonate	White, almost white crystalline powder	NC	NC	NC
22	PH + Magnesium stearate	White, almost white crystalline powder	NC	NC	NC
23	RC + STARCH	White, crystalline powder	NC	NC	NC
24	RC + STARCH PHOSPHATE	White, crystalline powder	NC	NC	NC
25	RC + Magnesium stearate	White, crystalline powder	NC	NC	NC
26	RC + PVPK30	White, crystalline powder	NC	NC	NC
27	RC +	White, crystalline powder	NC	NC	NC

NC- No Change

The physical compatibility study was performed visually. The study implies that the drug and excipients were physically compatible with each other as there was no change of physical description. The excipients which were compatible with the drugs were selected for formulation.

Chemical compatibility study

The possible interaction between the drug and the excipients used in the formulation was studied by FTIR spectroscopy. The results are given in figures and tables

FTIR SPECTROSCOPY OF DRUGS

Fig 13: FTIR of Rosuvastatin Calcium

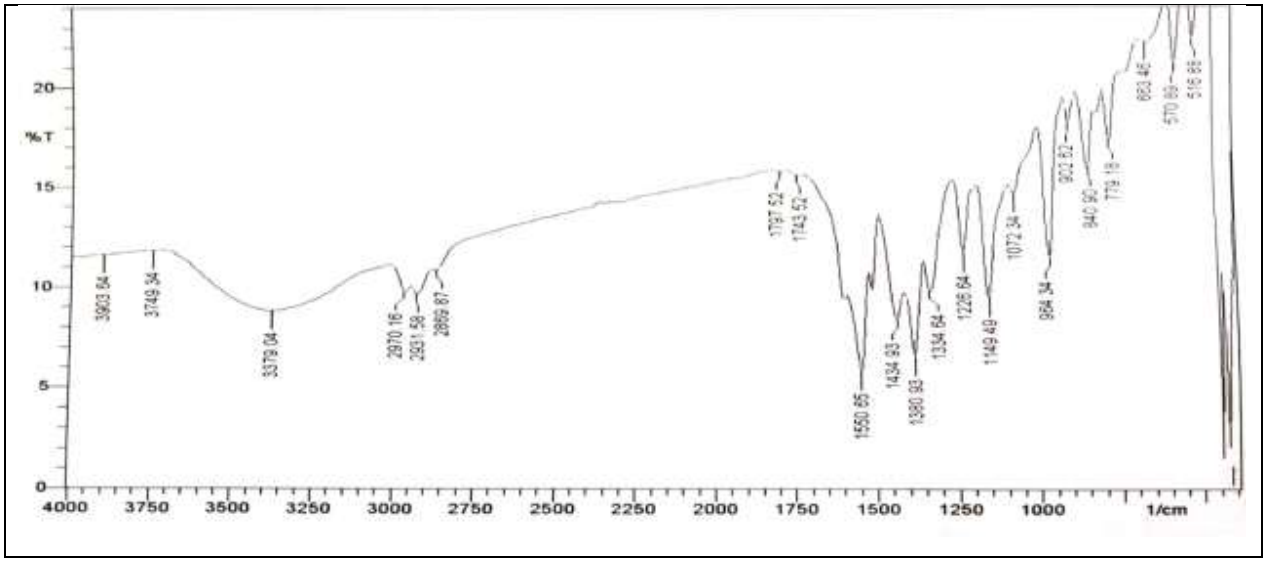


Table 9: IR Spectral interpretation of Rosuvastatin Calcium

Wave number (cm^{-1})	Interpretation
3363.61	Aromatic N-H stretching
1550.85	C=O stretching

Fig 14: FTIR of Propranolol Hydrochloride

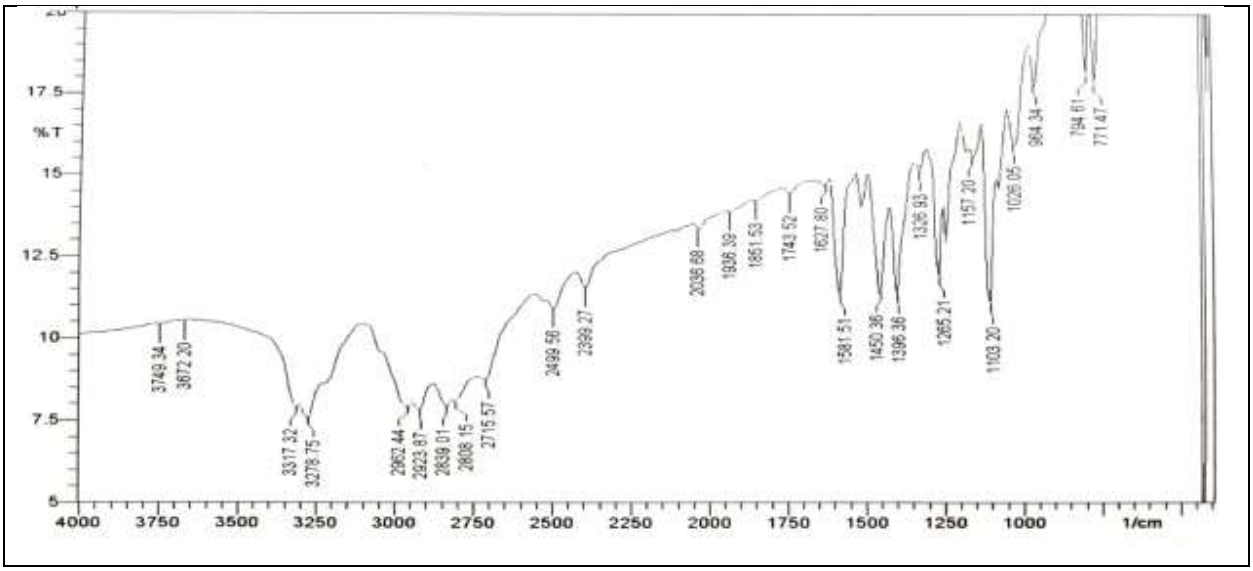


Table 10: IR Spectral interpretation of Propranolol hydrochloride

Wave number (cm^{-1})	**Interpretation**
3278.71	Secondary amine –NH stretching
2962	C–H stretching
1581.56	Aryl C ¼ C stretching
1265	Aryl O–CH2 asymmetric stretching
1026	Aryl O–CH2 symmetric stretching
794	Peak due to alpha-substituted naphthalene

Fig 15: FTIR Spectroscopy of Rosuvastatin Calcium with Starch Phosphate

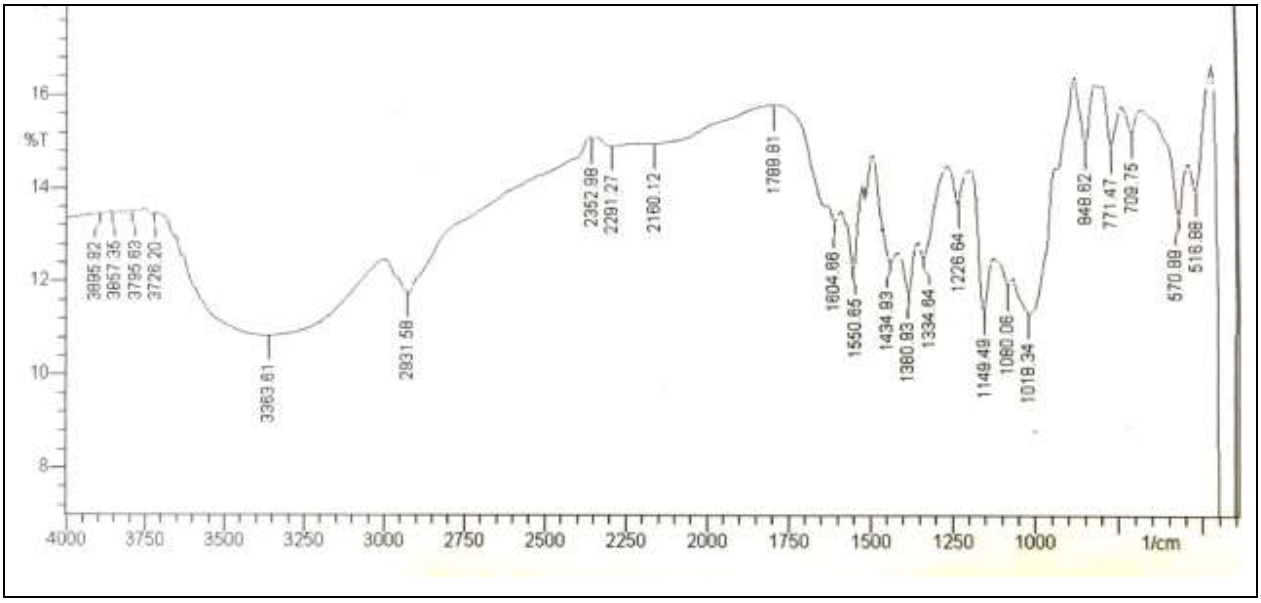


Table 11: IR Spectral interpretation of Rosuvastatin Calcium in the form of Starch Phosphate Solid Dispersion

Wave number (cm^{-1})	Interpretation
3363.61	Aromatic N-H stretching
1550.85	C=O stretching

The results of IR spectra of active ingredient and Excipient also revealed that there was no considerable change observed in bands of Rosuvastatin calcium. This shows the absence of any interaction between the drug and Starch phosphate.

Fig 16: FTIR Spectroscopy of Rosuvastatin Calcium with Polyvinyl pyrrolidone (PVP)

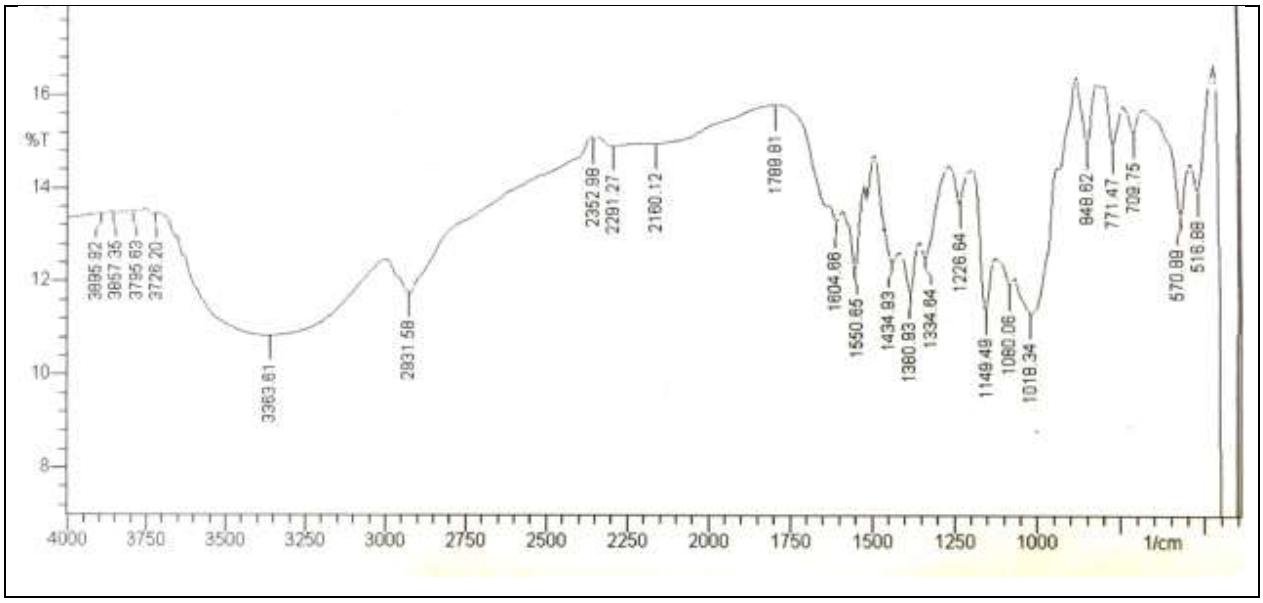


Table 12: IR Spectral interpretation of Rosuvastatin Calcium with Polyvinyl pyrrolidone (PVP)

Wave number (cm^{-1})	Interpretation
3363.61	Aromatic N-H stretching
1550.85	C=O stretching

The results of IR spectra of active ingredient and Excipient also revealed that there was no considerable change observed in bands of Rosuvastatin calcium. This shows the absence of any interaction between the drug and PVP K30.

Fig 17: FTIR Spectroscopy of Rosuvastatin Calcium with Sodium Starch Glycolate (SSG)

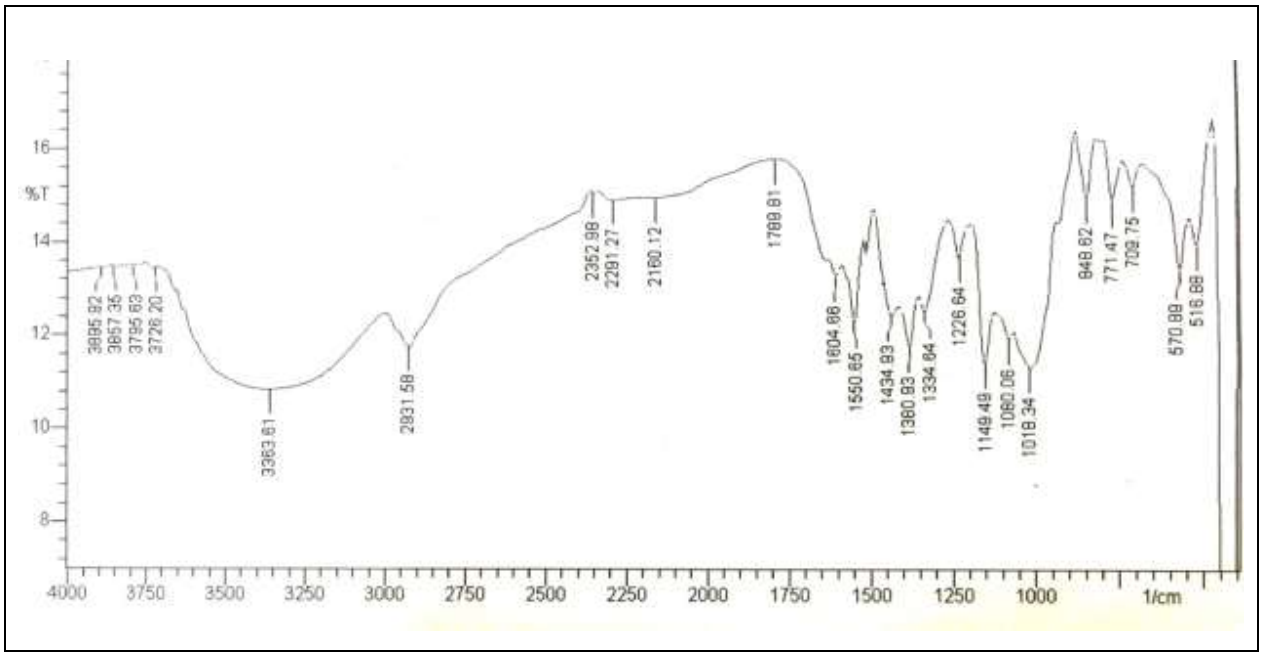


Table 13: IR Spectral Interpretation of Rosuvastatin Calcium with Sodium Starch Glycolate (SSG)

Wave number (cm^{-1})	Interpretation
3363.61	Aromatic N-H stretching
1550.85	C=O stretching

The results of IR spectra of active ingredient and Excipients also revealed that there was no considerable change observed in bands of Rosuvastatin calcium. This shows the absence of any interaction between the drug and SSG

PROPRANOLOL HYDROCHLORIDE FLOATING LAYER

FTIR SPECTROSCOPY OF DRUG AND EXCIPIENTS

Fig 18: FTIR of Propranolol with Ethyl Cellulose

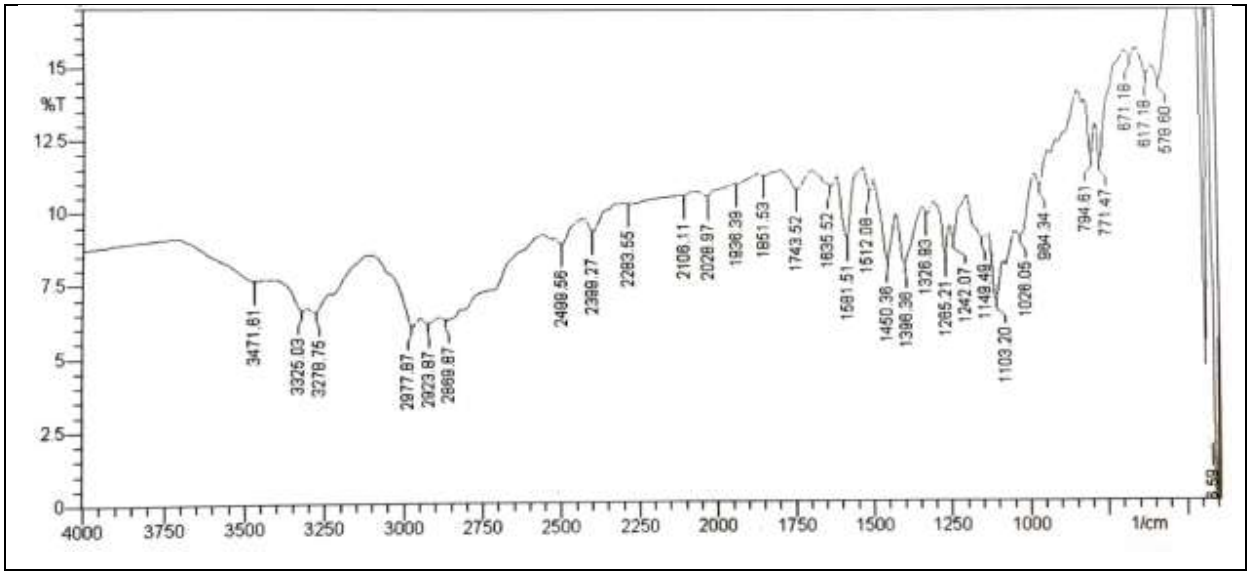


Table 14: IR Spectral interpretation of Propranolol with Ethyl Cellulose

Wave number (cm^{-1})	Interpretation
3278.75	Secondary amine –NH stretching
2923	C–H stretching
1581.56	Aryl C ¼ C stretching
1265	Aryl O–CH2 asymmetric stretching
1026	Aryl O–CH2 symmetric stretching
794	Peak due to alpha-substituted naphthalene

The spectra indicated that there was no drug – excipient interaction as the peaks of the drug and the other excipient were seen in the drug excipient mixture. The study implies that the active ingredients and the excipient are chemically compatible with each other as there was no change in the IR spectral peaks.

Fig 19: FTIR of Propranolol with Xanthan Gum

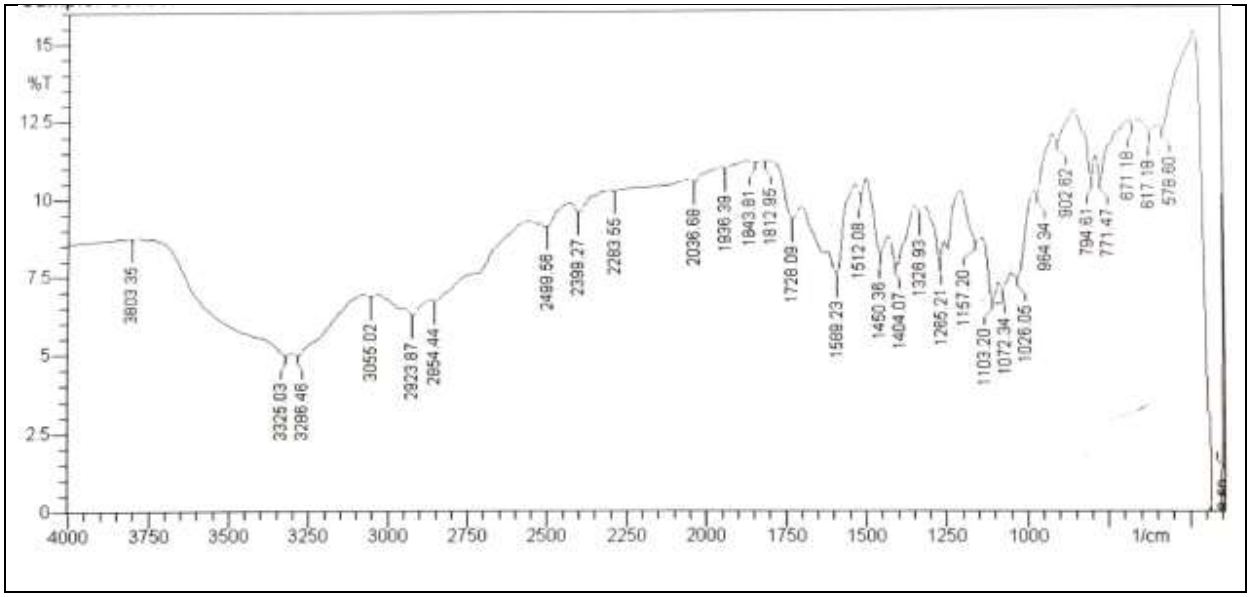


Table 15: IR Spectral interpretation of Propranolol with Xanthan Gum

Wave number (cm^{-1})	Interpretation
3286.46	Secondary amine –NH stretching
2923	C–H stretching
1589.56	Aryl C ¼ C stretching
1265	Aryl O–CH2 asymmetric stretching
1026	Aryl O–CH2 symmetric stretching
794	Peak due to alpha-substituted naphthalene

The spectra indicated that there was no drug – excipient interaction as the peaks of the drug and the other excipients were seen in the drug excipient mixture. The study implies that the active ingredients and the excipient are chemically compatible with each other as there was no change in the IR spectral peaks

Fig 20: FTIR of Propranolol with Micro Crystalline Cellulose

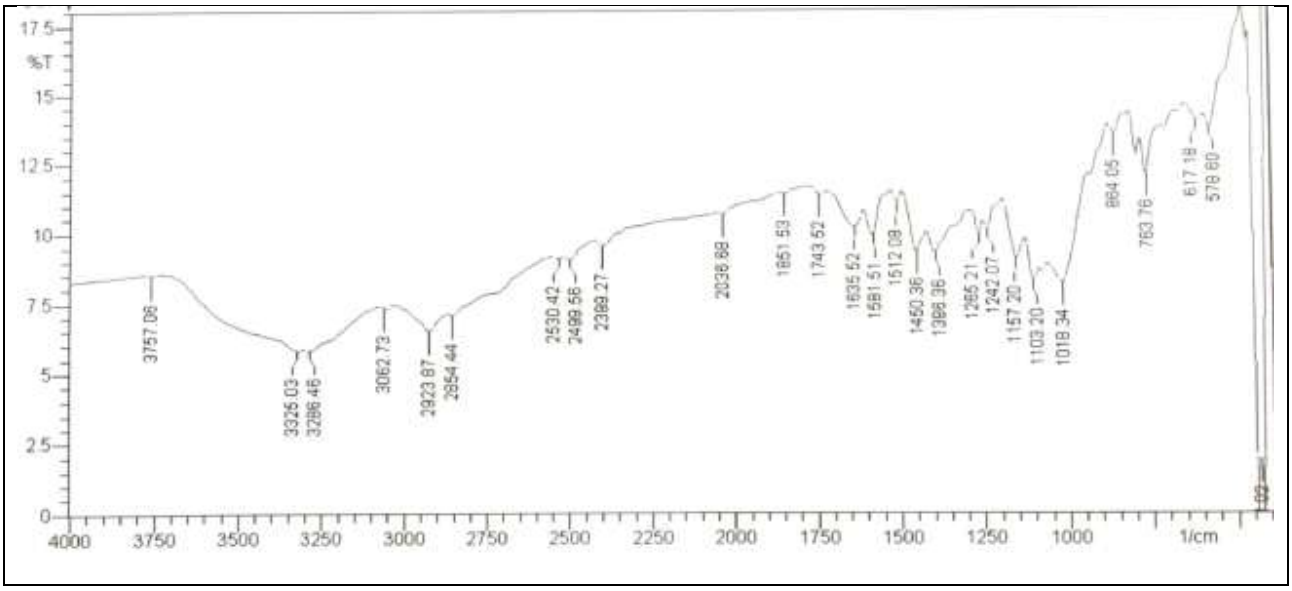


Table 16: IR Spectral Interpretation of Propranolol with Micro Crystalline Cellulose

Wave number (cm^{-1})	**Interpretation**
3286.46	Secondary amine –NH stretching
2923	C–H stretching
1589.56	Aryl C ¼ C stretching
1265	Aryl O–CH2 asymmetric stretching
1026	Aryl O–CH2 symmetric stretching
794	Peak due to alpha-substituted naphthalene

The spectra indicated that there was no drug – excipient interaction as the peaks of the drug and the other excipients were seen in the drug excipient mixture. The study implies that the active ingredients and the excipient are chemically compatible with each other as there was no change in the IR spectral peaks.

Fig 21: FTIR of Propranolol Hydrochloride with HPMC K4M

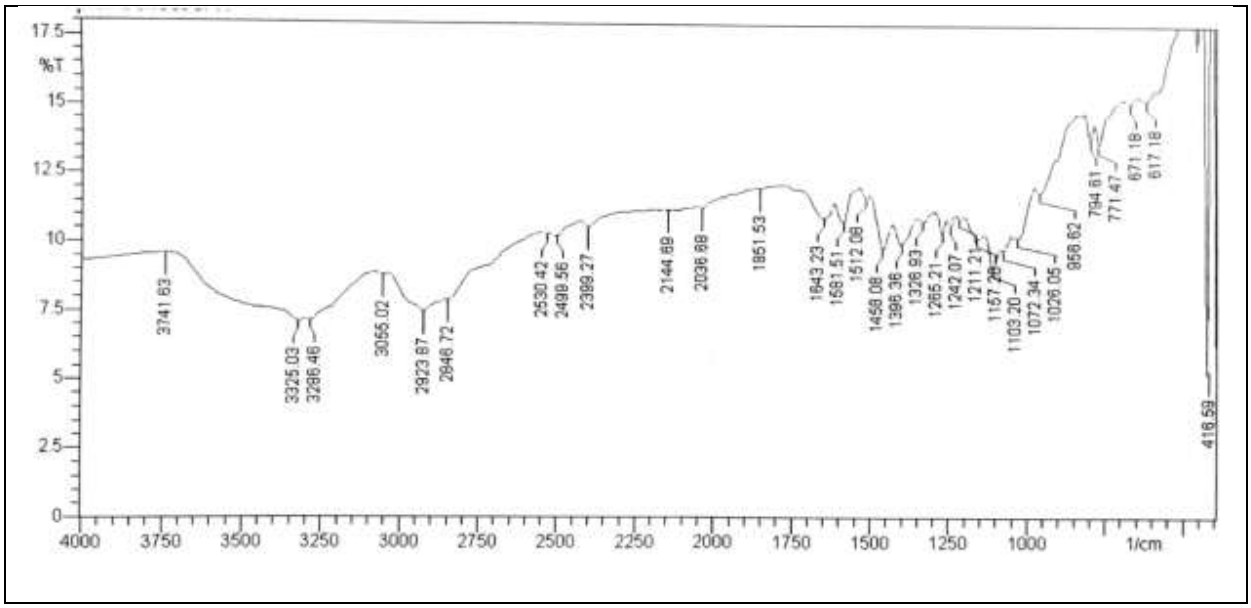


Table 17: IR Spectral Interpretation of Propranolol Hydrochloride with HPMC K4M

Wave number (cm^{-1})	Interpretation
3286.46	Secondary amine –NH stretching
2923	C–H stretching
1589.56	Aryl C ¼ C stretching
1265	Aryl O–CH2 asymmetric stretching
1026	Aryl O–CH2 symmetric stretching
794	Peak due to alpha-substituted naphthalene

The spectra indicated that there was no drug – excipient interaction as the peaks of the drug and the other excipients were seen in the drug excipient mixture. The study implies that the active ingredients and the excipient are chemically compatible with each other as there was no change in the IR spectral peaks.

Fig 22: FTIR of Propranolol Hydrochloride with HPMC K100

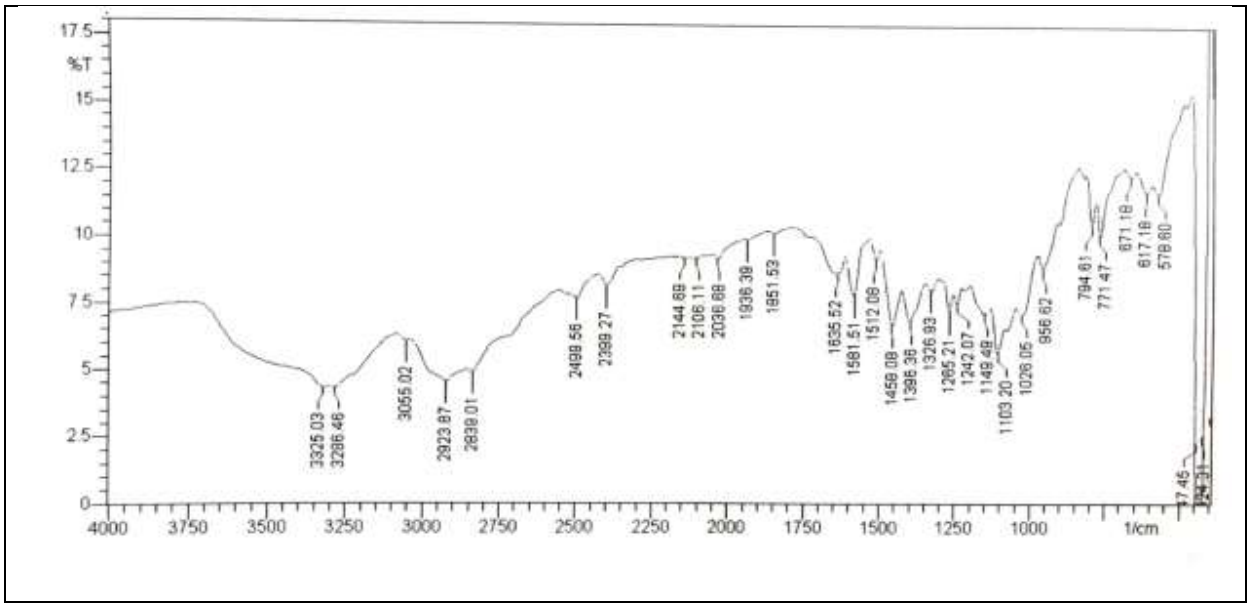


Table 18: IR Spectral Interpretation of Propranolol Hydrochloride with HPMC K100

Wave number (cm^{-1})	Interpretation
3286.46	Secondary amine –NH stretching
2923	C–H stretching
1589.56	Aryl C ¼ C stretching
1265	Aryl O–CH2 asymmetric stretching
1026	Aryl O–CH2 symmetric stretching
794	Peak due to alpha-substituted naphthalene

The spectra indicated that there was no drug – excipient interaction as the peaks of the drug and the other excipients were seen in the drug excipient mixture. The study implies that the active ingredients and the excipient are chemically compatible with each other as there was no change in the IR spectral peaks.

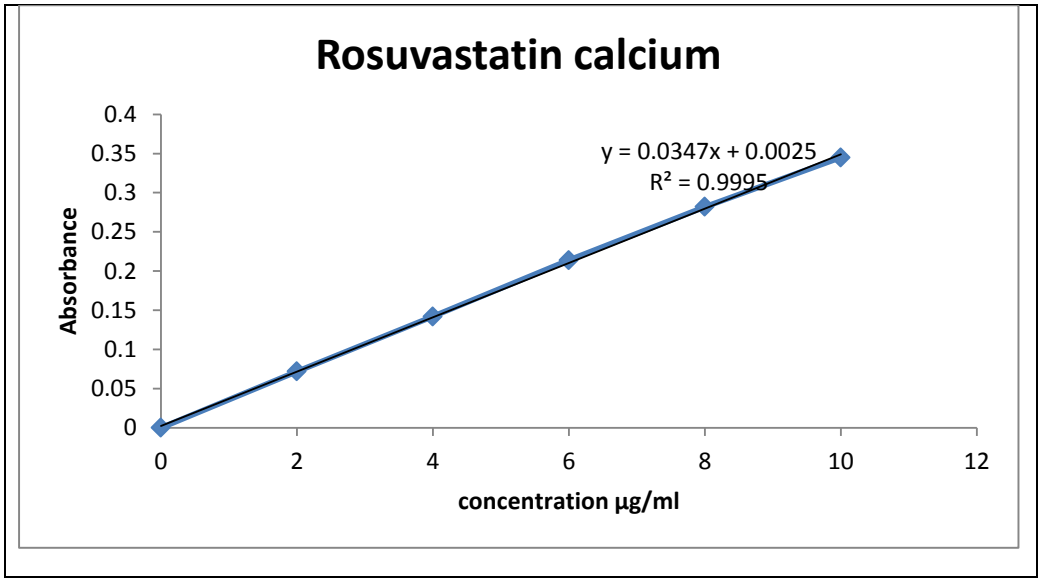
CALIBRATION CURVE:

The data for calibration curve of rosuvastatin calcium is given in table 19.

Table 19: Data of calibration curve of Rosuvastatin calcium in 0.1 N HCl.

Concentration (µg/ml)	Absorbance at λ_{290nm}
0	0
2	0.072
4	0.142
6	0.214
8	0.282
10	0.345

Fig 23: Calibration curve of Rosuvastatin calcium



It was found that the solutions of rosuvastatin calcium in 0.1 N HCl show linearity (R^2=0.9993) and obey beer Lambert's Law.

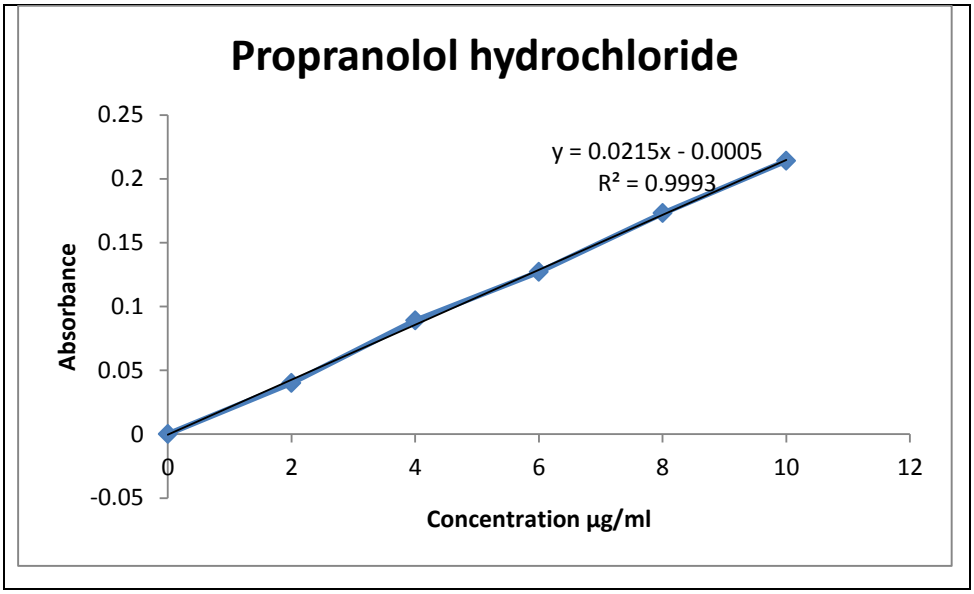
Calibration curve:

The data for calibration curve of propranolol hydrochloride is given in table 20.

Table 20: Data of calibration curve of Propranolol Hydrochloride in 0.1 N HCl.

Concentration (µg/ml)	Absorbance at λ_{290nm}
0	0
2	0.040
4	0.089
6	0.127
8	0.173
10	0.214

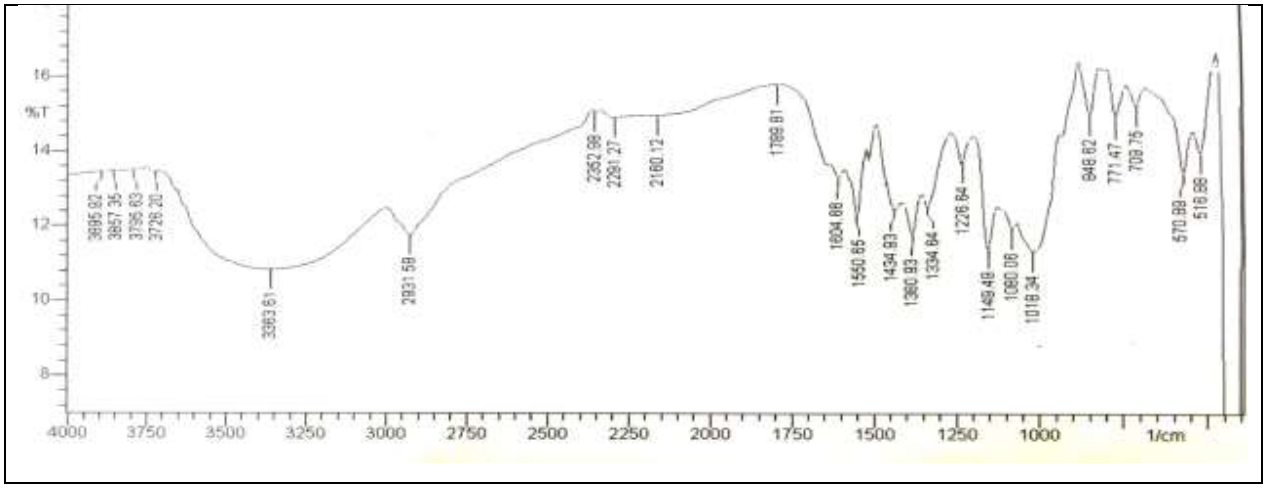
Fig 24: Calibration curve of Propranolol hydrochloride



It was found that the solutions of propranolol hydrochloride in 0.1 N HCl show linearity (R^2=0.9993) in absorbance at concentrations of 2-10 µg/ml and obey beer Lambert's Law.

FOR ROSUVASTATIN CALCIUM SOLID DISPERSION:

Fig 25: Fourier transforms infrared (FTIR) spectroscopy:



Determination of drug content:

The drug content of the solid dispersion of rosuvastatin calcium is given in the table 21

Table 21: Drug content of Rosuvastatin solid dispersion

Formulation	**% Drug content***
SD-1	99.55±0.180
SD-2	99.05±0.207
SD-3	97.49±0.456
SD-4	**96.98±0.342**

***Mean ±S.D (n=6)**

The drug content of solid dispersion was found to be within the Pharmacopoeial limits[58]

***Invitro* dissolution study:**

In vitro dissolution study of solid dispersion of rosuvastatin calcium is given in the table 22.

Table 22: *In Vitro* Dissolution study of solid dispersion of Rosuvastatin calcium

Time in minutes	Cumulative % drug release *			
	SD-1	SD-2	SD-3	SD-4
10	31.688±0.736	53.644±0.542	70.740±0.447	72.890±0.232
20	46.576±0.683	71.382±0.346	84.667±0.242	87.345±0.222
30	59.675±0.534	85.290±0.463	97.112±0.473	99.780±0.443
40	69.987±.323	95.106±0.574	**101.05±0.453**	**101.414±0.564**
50	89.565±.314	96.689±0.749		
60	**99.678±0.213**	**100.98±0.456**		

Solid dispersion SD-3 and SD-4 have better dissolution characteristics when compared with SD-1 and SD-2. So the Rosuvastatin calcium-Starch phosphate solid dispersion was taken in the ratios of 1:3 and 1:4 for compression into tablets for immediate release of Rosuvastatin calcium. Formulations SD-3 and SD-4 was found to be optimum for formulating tablets in order to enhance its solubility.

FOR IR FORMULATION:

PRECOMPRESSION STUDY:

The drug and the formulated blends are evaluated for Precompression parameters. The results are given in the table 23.

Table 23: Precompression study of drug and the formulated blends.

Drug formulation	Bulk density* g/cm^3	Tapped density* g/cm^3	Compressibility index*(%)	Hausner's ratio*	Angle of repose* (degree)
RC	0.401 ±0.003	0.566± 0.034	34.90±0.4563	1.542±0.0045	42.909±0.3246
RC-1	0.384 ±0.008	0.588 ±0.011	34.69 ±0.4073	1.531 ±0.0038	41.030 ±0.1120
RC-2	0.375 ±0.0042	0.598 ±0.013	35.02 ±0.3425	1.456 ±0.0034	42.340 ±0.4025
RC-3	0.421 ±0.0003	0.573 ±0.017	34.21 ±0.4563	1.512 ±0.0023	41.393 ±0.4630

The bulk density of IR Blends ranged from 0.384- 0.421 g/cm^3 and tapped density ranged from 0.573- 0.598 g/cm^3. The compressibility index of the IR granules ranged from 34.21-35.02% and Hausner's ratio ranged from 1.456-1.531. The angle of repose of IR granules ranged from 41.03-41.39. The formulated blends show poor flow property. So wet granulation technique is used for preparing IR granules Rosuvastatin calcium.

The IR granules were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. The results are given in the table 24.

Table 24: Precompression study of immediate release granules.

Drug formulation	Bulk density* g/cm^3	Tapped density* g/cm^3	Compressibility index*(%)	Hausner's ratio*	Angle of repose* (degree)
RC-1	0.354 ±0.0018	0.558 ±0.041	16.69 ±0.3073	1.151 ±0.0018	32.030 ±0.2120
RC-2	0.345 ±0.0032	0.588 ±0.023	15.02 ±0.2425	1.136 ±0.0024	31.340 ±0.3025
RC-3	0.371 ±0.0023	0.553 ±0.007	15.21 ±0.3563	1.101 ±0.0013	30.393 ±0.5630

The bulk density of IR Blends ranged from 0.345- 0.371 g/cm^3 and tapped density ranged from 0.553- 0.588 g/cm^3. The compressibility index of the IR granules ranged from 31.02-33.69% and Hausner's ratio ranged from 1.136-1.151. The angle of repose of IR granules ranged from 30.393- 32.030. The formulated IR granules show good flow property.

Formulation development:

Preparation of IR tablets of rosuvastatin calcium:

Immediate release solid dispersion compressed layer of rosuvastatin calcium was prepared by wet granulation method.

The formulations of immediate release solid dispersion layer of Rosuvastatin calcium (RC-1, RC-2 and RC-3) were prepared using the super disintegrant sodium starch glycolate.

The formulation were compressed on a 10 station tablet compression machine using 10/32 concave punches.

POST COMPRESSION STUDY

UNIFORMITY OF WEIGHT[58]:

The uniformity of weight of the formulated tablets is given in the table 25.

Table 25: Uniformity of weight of the formulated tablets.

Formulation	Uniformity of weight(mg)*
RC-1	150.55±0.2315
RC-2	152.55±0.3232
RC-3	**150.60±0.2211**

***MEAN±S.D (n=20)**

The tablets comply with the test for uniformity of weight.

TABLET THICKNESS AND DIAMETER[71]:

The thickness and diameter of the formulated tablets is given in the table 26

Table 26: Thickness and Diameter of the formulated tablets.

Formulation	Thickness (mm)*	Diameter(mm)*
RC-1	2.500±0.0038	8.000±0.0031
RC-2	2.500±0.0087	8.000±0.0045
RC-3	**2.500±0.0024**	**8.000±0.0076**

***MEAN±S.D (n=10)**

The tablets have uniform thickness and diameter.

HARDNESS[71]:

The hardness of the formulated tablets is given in the table 27

Table 27: Hardness of the formulated tablets

Formulation	Hardness Kg/cm^2*
RC-1	4.15±0.264
RC-2	4.10±0.255
RC-3	**3.75±0.238**

***MEAN±S.D (n=10)**

All the formulated tablets showed sufficient mechanical strength to resist the transportation.

FRIABILITY[71]:

The Friability of the formulated tablets is given in the table 28

Table 28: Friability of the formulated tablets

Formulation	Friability *
RC-1	0.320±0.0062
RC-2	0.289±0.0102
RC-3	**0.295±0.0053**

***MEAN±S.D (n=20)**

The percentage friability of all the formulation was within acceptable limits[71].

DRUG CONTENT[48]:

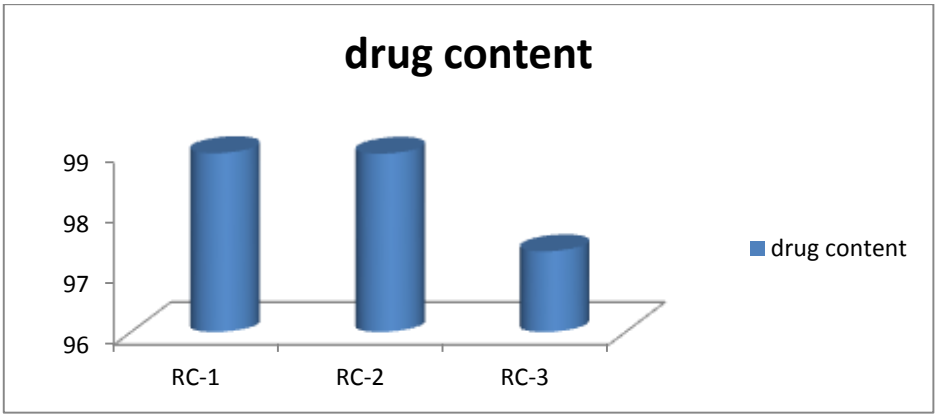
The Drug content of the formulated IR tablets is given in the table 29 and Fig 26

Table 29: Drug content of the formulated IR tablets

Formulation	% Drug content *
RC-1	98.95±0.0042
RC-2	98.94±0.0052
RC-3	**97.33±0.0063**

***MEAN±S.D (n=6)**

Fig 26: Drug content of the formulated IR tablets



The drug content of the IR tablets was within Pharmacopoeial limits[58].

DISINTEGRATION TIME[58]:

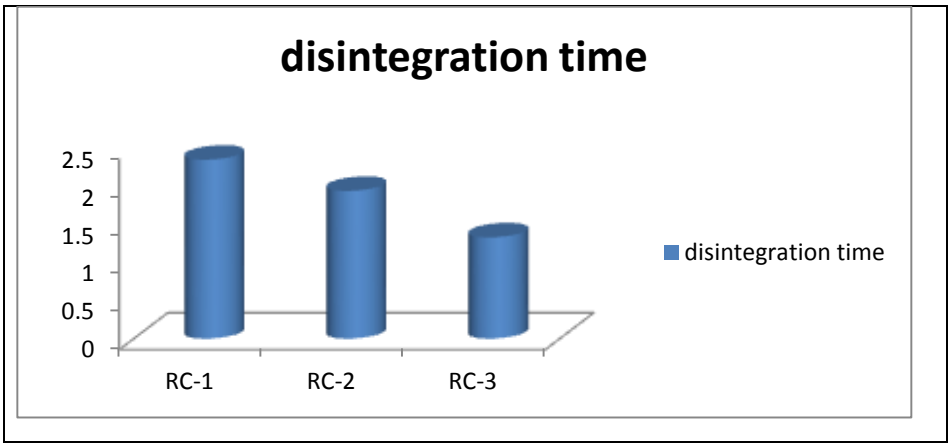
The disintegration time of the IR tablets is given in the table 30 and Fig 27.

Table 30: Disintegration time of the IR tablets

Formulation	Disintegration time(minutes) *
RC-1	2.35±0.0142
RC-2	1.94±0.0072
RC-3	1.33±0.0033

*MEAN±S.D (n=6)

Fig 27: Disintegration time of the IR tablets



The disintegration time of the IR tablets ranged from 1.33 to 2.35 minutes. The disintegration time of IR tablets containing solid dispersion of Rosuvastatin calcium-Starch phosphate in the ratio of 1:4 was found to be optimum for immediate disintegration of IR tablets.

INVITRO DISSOLUTION STUDY[40]:

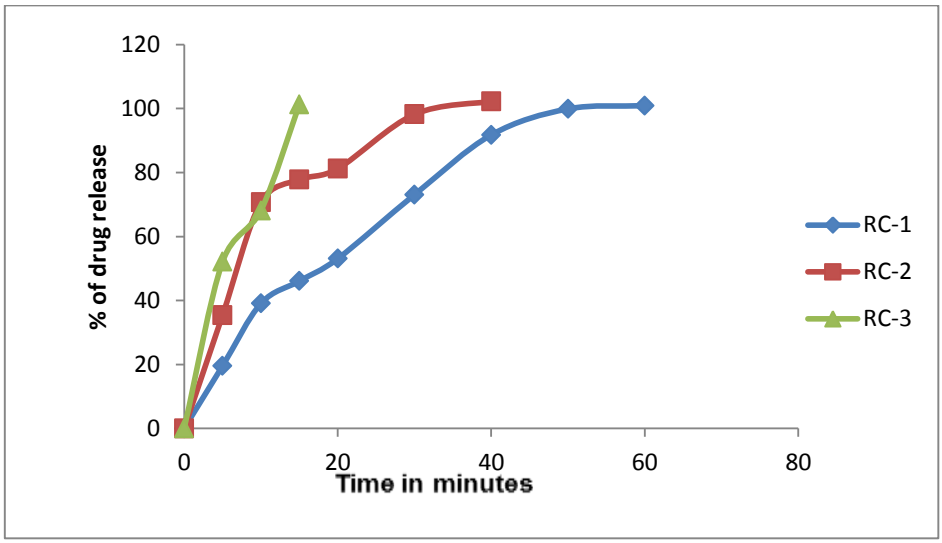
The *invitro* dissolution of immediate release formulations of Rosuvastatin calcium is given in the Table 31 and Fig 28

Table 31: *invitro* dissolution of immediate release formulation of Rosuvastatin calcium

Time in Minutes	Cumulative % drug release*		
	RC-1	**RC-2**	**RC-3**
5	19.525	35.370	52.081
10	39.057	70.740	68.120
15	46.057	77.790	**101.292**
20	53.058	81.189	
30	73.060	98.209	
40	91.760	**102.190**	
50	99.890		
60	**100.908**		

*MEAN±S.D (n=6)

Fig 28: *invitro* dissolution of immediate release formulation of Rosuvastatin calcium



The *invitro* dissolution of IR tablets showed that solid dispersion enhanced the dissolution of rosuvastatin calcium when compared to the conventional tablet RC-1. The solid dispersion tablet (RC-3) released the drug faster when compared to RC-2. Therefore formulation RC-3 was found optimum and selected for bilayer floating tablets.

FOR BILAYER FLOATING TABLETS:

PRECOMPRESSION STUDY:

The drug and the formulated blends of SR were evaluated for Precompression parameters. The results are given in the table 31.

Table 32: **Precompression study of drug and formulated blends**[71]

Drug formulation	Bulk density* g/cm^3	Tapped density* g/cm^3	Compressibility index*(%)	Hausner's ratio*	Angle of repose* (degree)
PH	0.500 ±0.0008	0.769 ±0.031	34.69 ±0.3073	1.538±0.0018	40.220±0.2143
SR-1	0.367 ±0.0032	0.581 ±0.043	34.04 ±0.3016	1.181±0.0067	34.080 ±0.4120
SR-2	0.323 ±0.0042	0.542 ±0.018	31.02 ±0.5425	1.136 ±0.0034	34.340 ±0.5025
SR-3	0.341 ±0.0031	0.510 ±0.007	32.21 ±0.4563	1.121 ±0.0043	32.393 ±0.3630
SR-4	0.340±0.0028	0.505±0.002	32.10±0.4102	1.164±0.0032	32.768±0.3426
SR-5	0.356±0.0067	0.549±0.024	33.34±0.4201	1.149±0.0045	34.909±0.5625
SR-6	0.342±0.0059	0.532±0.016	32.21±0.3520	1.120±0.0019	32.192±0.3542
SR-7	0.321±0.0043	0.514±0.025	31.25±0.3211	1.140±0.0024	32.324±0.2110

*MEAN±S.D (n=6)

The bulk density of SR granules ranged from 0.321- 0.367 g/cm^3 and tapped density ranged from 0.505- 0.581 g/cm^3. The compressibility index of the SR granules ranged from 31.02-34.64 and

Hausner's ratio ranged from 1.121-1.191. The angle of repose of SR granules ranged from 32.192-34.909. The formulated SR granules show good flow property.

FORMULATION DEVELOPMENT

PREPARATION OF REGIO-SELECTIVE BILAYER FLOATING TABLETS

- Preparation of rosuvastatin starch phosphate solid dispersion
- Optimized immediate release layer of rosuvastatin solid dispersion was prepared by wet granulation
- Regio-selective sustained release layer of propranolol hydrochloride was prepared by wet granulation method

Bilayer floating tablets of propranolol hydrochloride and rosuvastatin calcium solid dispersion was prepared by compressing the optimized formula of IR solid dispersion granules with various formulations of SR granules on a 10 station tablet compression machine using 12/32 concave punches

POST COMPRESSION STUDIES OF BILAYER FLOATING TABLETS:

UNIFORMITY OF WEIGHT[58]:

The uniformity of weight of the formulated tablets is given in table 33.

Table 33: Uniformity of weight of the formulated tablets.

Formulation	Uniformity of weight(mg)*
RBFT-1	400.25±0.1215
RBFT-2	400.15±0.1232
RBFT-3	400.60±0.1111
RBFT-4	400.65±0.1115
RBFT-5	400.85±0.1012
RBFT-6	400.20±0.1121
RBFT-7	**400.30±0.1201**

***MEAN±S.D (n=20)**

The tablets comply with the test for uniformity of weight.

TABLET THICKNESS AND DIAMETER[71]:

The thickness and diameter of the formulated tablets is given in table 34.

Table 34: thickness and diameter of the formulated tablets.

Formulation	Thickness (mm)*	Diameter(mm)*
RBFT-1	3.950±0.0084	9.500±0.0327
RBFT-2	3.945±0.0032	9.510±0.0119
RBFT-3	3.854±0.0056	9.530±0.0312
RBFT-4	4.007±0.0089	9.550±0.0167
RBFT-5	3.960±0.0023	9.510±0.0253
RBFT-6	3.890±0.0052	9.537±0.0234
RBFT-7	**3.850±0.0043**	**9.510±0.0127**

***MEAN±S.D (n=10)**

The tablets have uniform thickness and diameter.

HARDNESS[71]:

The hardness of the formulated tablets is given in table 35.

Table 35: Hardness of the formulated tablets

Formulation	Hardness Kg/cm^2*
RBFT-1	5.15±0.264
RBFT-2	5.10±0.155
RBFT-3	5.75±0.238
RBFT-4	5.64±0.164
RBFT-5	5.21±0.255
RBFT-6	5.90±0.138
RBFT-7	**5.29±0.264**

***MEAN±S.D (n=10)**

All the formulated tablets showed sufficient mechanical strength to resist the transportation.

FRIABILITY[71]:

The Friability of the formulated tablets is given in the table 36

Table 36: Friability of the formulated tablets

Formulation	Friability *
RBFT-1	0.220±0.0022
RBFT-2	0.389±0.0122
RBFT-3	0.295±0.0033
RBFT-4	0.320±0.0042
RBFT-5	0.389±0.0102
RBFT-6	0.395±0.0033
RBFT-7	**0.345±0.0029**

***MEAN±S.D (n=20)**

The percentage friability of all the formulation was within Pharmacopoeial limits[58].

***INVITRO* FLOATING STUDIES:**

The *invitro* floating characteristics of the formulated bilayer floating tablets is given in table 37 and Fig 37

Table 37: *Invitro* floating characteristics of the formulated bilayer floating tablets

FORMULATION	FLOATING LAG TIME(MINUTES)	FLOATING DURATION(HOURS)
RBFT-1	2.50±0.045	11.30±0.112
RBFT-2	2.10±0.045	12.43±0.103
RBFT-3	1.89±0.118	12.30±0.313
RBFT-4	1.76±0.218	12.46±0.212
RBFT-5	2.03±0.220	12.05±0.271
RBFT-6	1.39±0.210	12.34±0.231
RBFT-7	**1.03±0.231**	**12.59±0.023**

***MEAN±S.D (n=6)**

Fig 29: *Invitro* floating lag time of RBFT

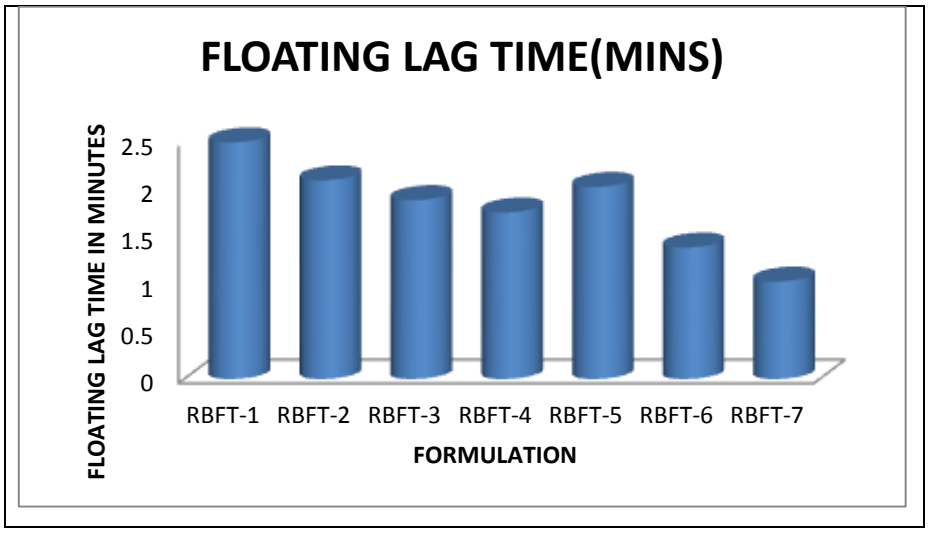
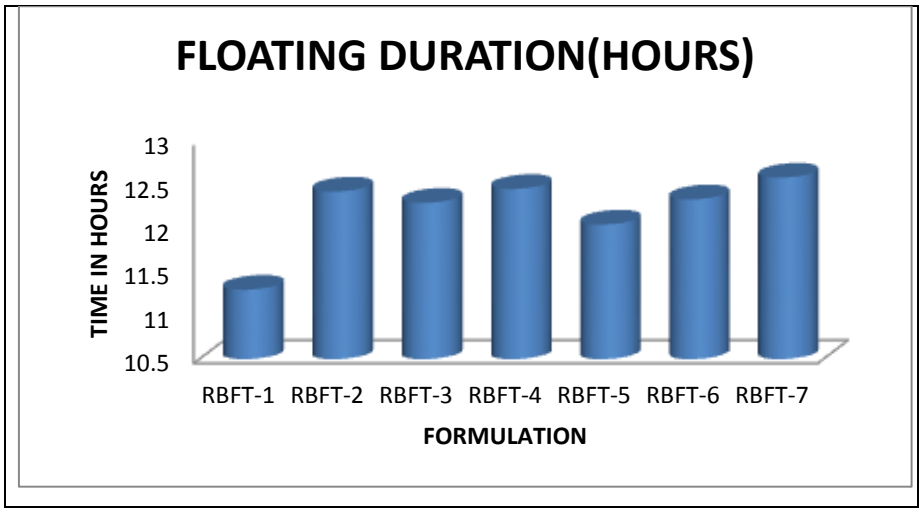
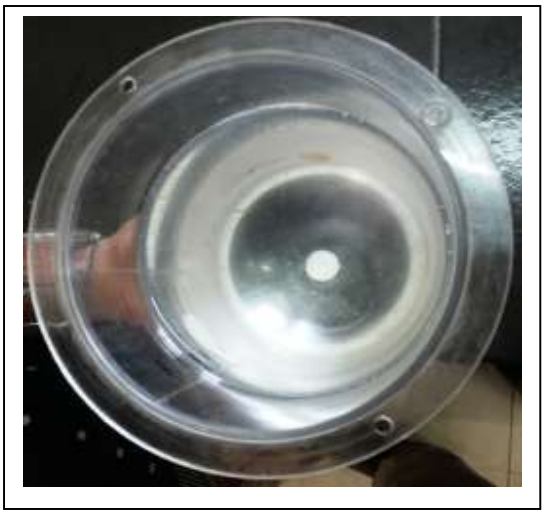


Fig 30: *Invitro* floating duration of RBFT



The floating duration ranged from 11.39 to 12.59 hours and the floating lag time ranged from 1.03 to 2.50 minutes. The matrix integrity of the prepared floating tablets is good during the floating study. The formulation RBFT-7 exhibits optimum floating behavior when compared with all the other formulation.

Buoyancy test at 30 minutes



Buoyancy test at 12th hour

BIAYER FLOATING TABLETS

DRUG CONTENT OF BILAYER FLOATING TABLET BY SIMULTANEOUS ESTIMATION METHOD:

The drug content of propranolol hydrochloride and rosuvastatin calcium of the formulated bilayer floating tablets is given in table 38 and Fig 31 and 32.

Table 38: Drug content of Bilayer floating tablet

Formulation	% DRUG CONTENT*	
	Rosuvastatin calcium	Propranolol hydrochloride
RBFT-1	99.25±0.045	102.25±0.245
RBFT-2	101.05±0.290	103.05±0.190
RBFT-3	99.93±0.101	103.00±0.118
RBFT-4	99.46±0.192	99.46±0.241
RBFT-5	97.89±0.073	97.89±0.189
RBFT-6	99.45±0.112	100.52±0.100
RBFT-7	**104.30±0.036**	**101.53±0.021**

***MEAN±S.D (n=6)**

Fig 31: Drug content of rosuvastatin calcium in RBFT

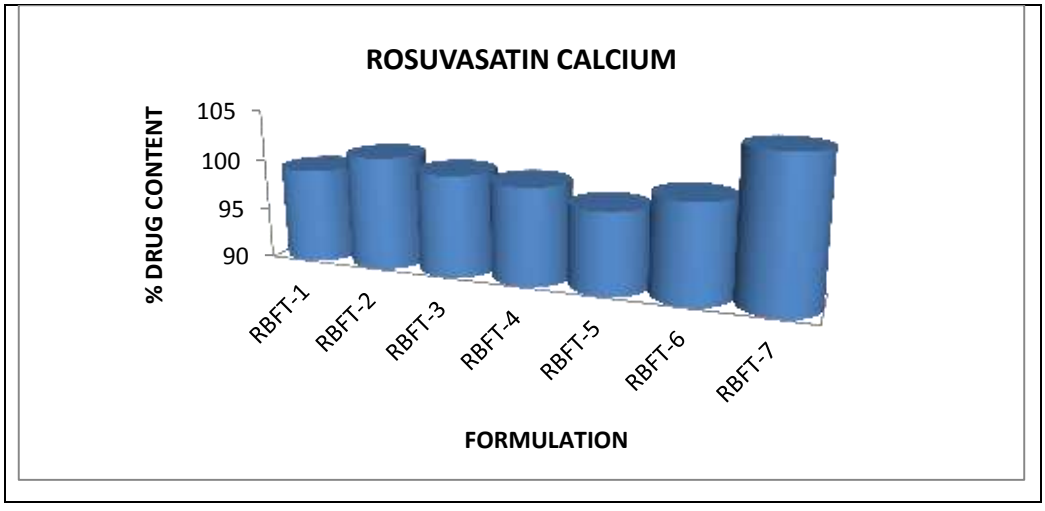
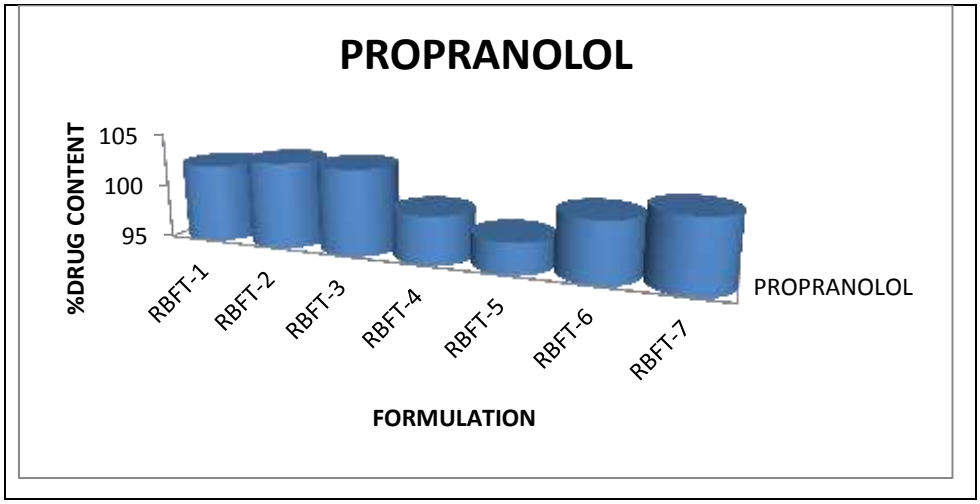


Fig 32: drug content of Propranolol hydrochloride in RBFT



The drug content of rosuvastatin calcium and propranolol hydrochloride in bilayer floating tablet was found to be within the Pharmacopoeial limits[58].

***IN VITRO* DISSOLUTION STUDY:**

The *invitro* dissolution of drugs in the bilayer floating tablets is given in table 39,40 and fig 33.

Table 39: *invitro* dissolution of rosuvastatin calcium in RBFT

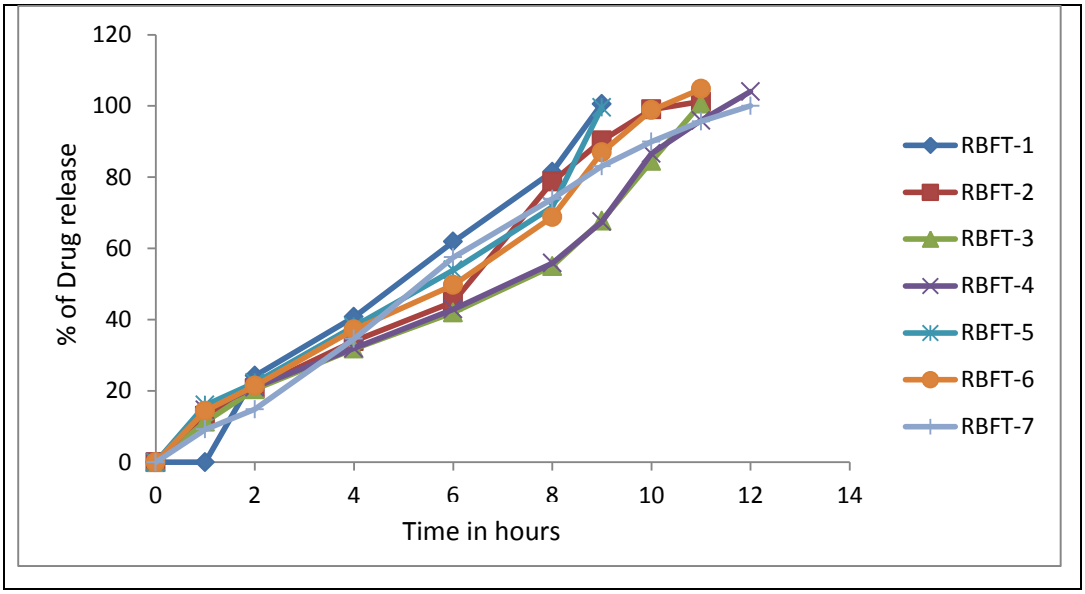
TIME (MINUTES)	CUMULATIVE % ROSUVASTATIN CALCIUM RELEASE*						
	RBFT-1	**RBFT-2**	**RBFT-3**	**RBFT-4**	**RBFT-5**	**RBFT-6**	**RBFT-7**
5	52.79±0.003	52.97±0.323	52.97±0.093	52.34±0.003	52.43±0.210	52.46±0.211	52.08±0.042
10	68.30±0.034	67.73±0.324	68.48±0.024	68.87±0.420	68.46±0.201	68.75±0.262	68.12±0.033
15	101.43±0.032	101.91±0.740	101.78±0.051	101.90±0.210	101.23±0.043	101.34±0.082	101.29±0.134

***MEAN±S.D (n=6)**

Table 40: *Invitro* dissolution study of propranolol hydrochloride in RBFT

TIME (Hours)	CUMULATIVE % PROPRANOLOL HYDROCHLORIDE RELEASE*						
	RBFT-1	**RBFT-2**	**RBFT-3**	**RBFT-4**	**RBFT-5**	**RBFT-6**	**RBFT-7**
1	`16.07±0.034	12.98±0.052	11.32±0.21	14.64±0.022	16.02±0.046	14.43±0.045	09.22±0.076
2	24.24±0.032	20.72±0.084	20.45±0.045	21.04±0.034	22.33±0.043	21.43±0.050	14.85±0.094
3	31.08±0.052	28.19±0.121	23.76±0.023	23.00±0.012	31.36±0.013	28.41±0.090	23.47±0.023
4	40.77±0.021	33.99±0.092	31.86±0.052	31.99±0.054	38.09±0.018	37.26±0.056	34.63±0.043
5	48.23±0.023	39.59±0.012	41.61±0.053	36.78±0.089	46.66±0.017	43.57±0.043	46.90±0.026
6	61.88±0.362	45.05±0.034	42.01±0.089	42.94±0098	53.93±0.034	49.73±0.021	57.51±0.056
7	65.75±0.021	62.04±0.027	51.71±0.037	51.67±0.034	63.19±0.032	60.53±0.034	67.49±0.094
8	81.52±0.024	78.75±0.054	55.05±0.054	55.88±0.032	71.69±0.052	68.82±0.021	73.91±0.043
9	**100.54±0.078**	90.28±0.065	67.79±0.089	67.47±0.043	**99.58±0.074**	86.94±0.054	83.06±0.023
10		99.00±0.075	84.53±0.056	86.66±0.024		98.82±0.067	89.97±0.045
11		**101.26±0.073**	**100.64±0.035**	95.90±0.078		**104.77±0.057**	95.64±0.086
12				**104.03±0.033**			**100.01±0.014**

Fig 33: *Invitro* dissolution study of propranolol hydrochloride in RBFT



The results of invitro dissolution study of regio-selective bilayer floating tablets showed that the formulation RBFT-1, RBFT-2 and RBFT-3 containing HPMC K100 polymer released the entire drug within 9,10 and 11 hours respectively. The formulations RBFT-5, RBFT-6 and RBFT-7 containing HPMC K4M polymer have sustained the drug release from the bilayer floating tablet for more hours (11,11 and 12 hours respectively). Though HPMC K100 were added in more amount in the formulations RBFT-1, RBFT-2, RBFT-3 and RBFT-4 the release of the drug from the tablet was not sustained for more hours when compared with formulations RBFT-5, RBFT-6 and RBFT-7 in which HPMC K4M were present. All the formulations contain ethyl cellulose, xanthan gum in similar quantities. The only variable adjusted was the HPMC K4M and HPMC K100. In case of RBFT-4 the polymer HPMCK100 was sustained the drug release over period of 12 hours in higher concentrations then that of all other formulations. It was concluded that the formulation RBFT-7 containing HPMC K4M in 20% was found to be the best formulation to sustain the release of the drug over the period of 12 hours. Other formulation released the drug before 12 hours. Therefore RBFT-7 can be the best formulation.

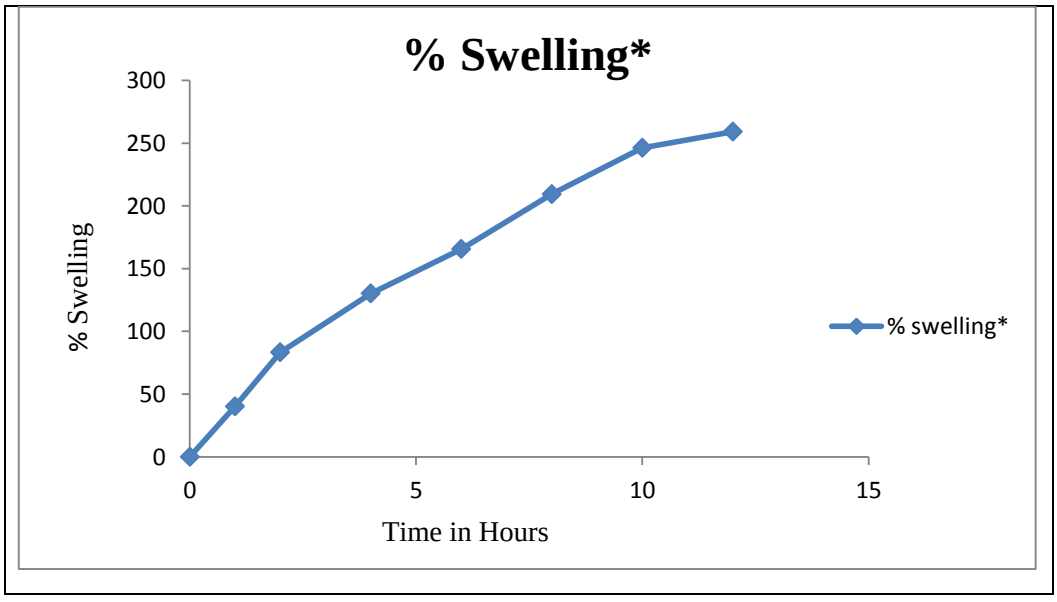
SWELLING STUDIES:

Swelling study was carried out on the optimized bilayer floating tablets. The % swelling of the tablets is given in the table 41 and fig 34

Table 41: swelling index of optimized formulation

Time in hours	% swelling*
0	0
1	40.32
2	83.26
4	130.14
6	165.67
8	209.42
10	246.20
12	259.19

Fig 34: swelling index of optimized formulation



The swelling index of the bilayer floating tablets showed that the floating matrix layer maintained their integrity and increased swelling during the study. The study showed that the combination of HPMC K4M and Xanthan gum polymers has higher swelling index. More swelling resulted in more retarded release of the drug from the matrix layer

***INVITRO* RELEASE KINETICS:**

The values obtained from *invitro* dissolution of Propranolol hydrochloride from bilayer floating tablet were fitted in various kinetic models. The results are given in table 42 and Figure 34,35,36,37 and 38.

Table 42: *Invitro* Release Kinetics of BFT

Time in Hours	% Cum. Drug release	% Cum. Drug remaining	Log% Cum. drug remaining	Square root of time	Log time	Log% cum. Drug release	Cube root of % drug remaining
0	0	100	2.00000	0	∞	∞	4.641588
1	9.226	90.774	1.95796	1.00000	0	0.965013	4.494214
2	14.859	85.141	1.93013	1.41421	0.30102	1.171989	4.399259
3	23.471	76.529	1.88382	1.73205	0.47712	1.370531	4.245628
4	34.631	65.369	1.81537	2.00000	0.60205	1.539465	4.028319
5	46.906	53.094	1.72504	2.23606	0.69897	1.671228	3.758505
6	57.516	42.484	1.62822	2.44940	0.77815	1.759788	3.489328
7	67.490	32.510	1.51201	2.64575	0.84509	1.829239	3.191579
8	73.916	26.084	1.41637	2.82840	0.90308	1.868738	2.965683
9	83.064	16.936	1.22881	3.00000	0.95424	1.919412	2.568050
10	89.978	10.022	1.00095	3.16224	1.00000	1.954136	2.156013
11	95.647	4.353	0.63878	3.31662	1.04139	1.980671	1.632787
12	99.195	0.0150	0.09420	3.46413	1.07918	1.996489	0.246621

Fig 34: Zero order release kinetics

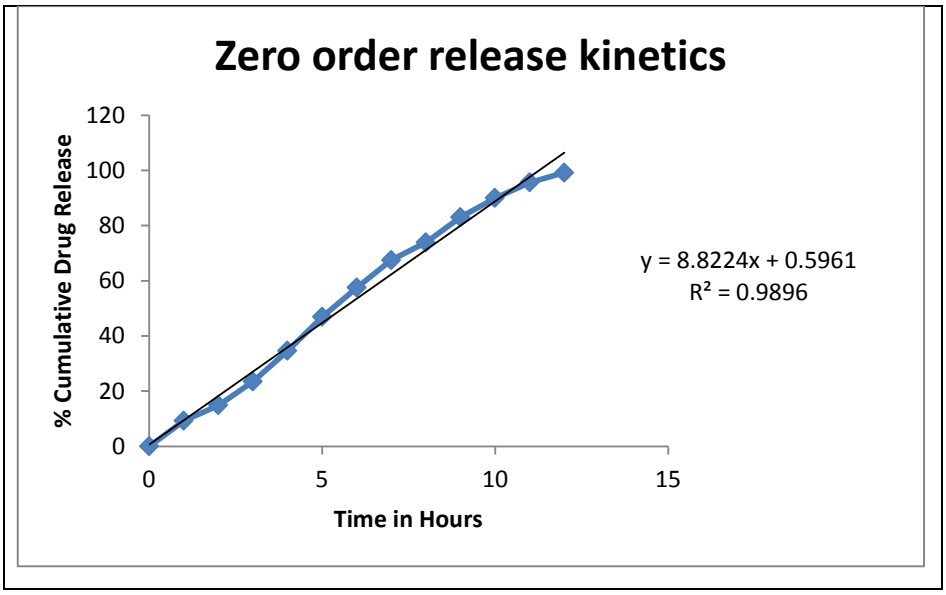


Fig 35: First order release kinetics

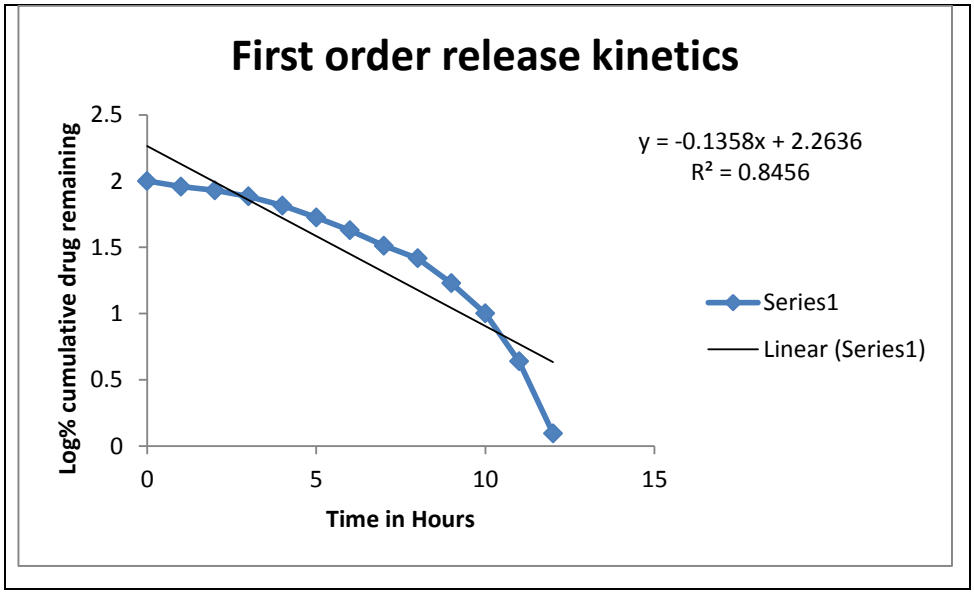


Fig 36: Higuchi Diffusion kinetics

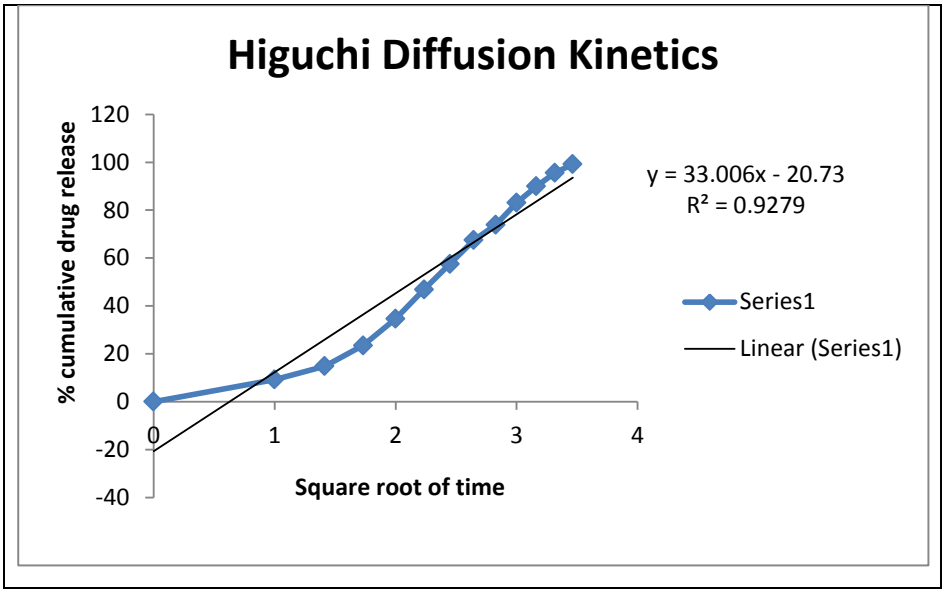


Fig 37: Korsmeyer Peppas Equation

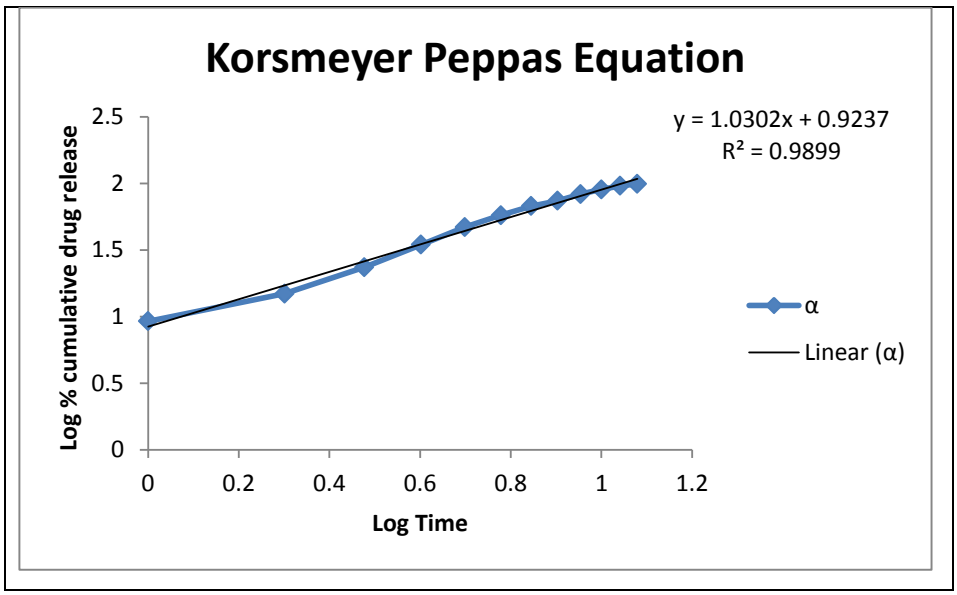
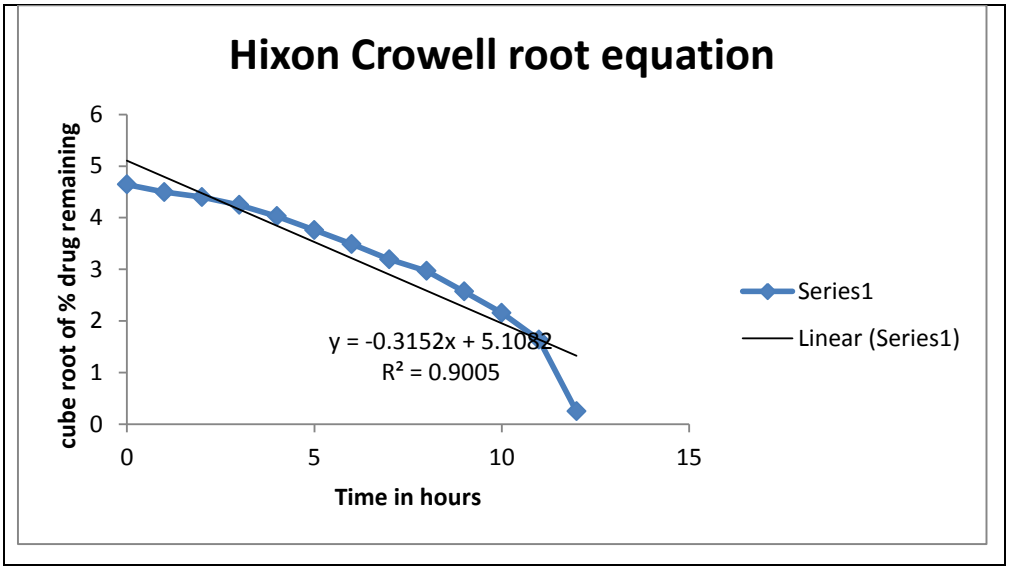


Fig 38: Hixon Crowell cube root equation



Determination of drug release mechanism of optimized bilayer floating tablets:

- The order of release of drug was found to be zero order, in which R^2 value was close to 1.
- The n value of Korsmeyer Peppas equation was found to be 1.0302. It was concluded that the release followed non- Fickian transport.
- Good correlation coefficients are obtained for Hixon Crowell cube root and Higuchi equation. Propranolol hydrochloride is a hydrophilic drug with a hydrophilic matrix
- Swelling and hydration of the polymer matrix, Dissolution of the drug in the polymer matrix and diffusion of the drug through the polymer plays role in the drug release. The results showed that the formulation followed zero order release

STABILITY STUDY:

The optimized bilayer floating tablets were subjected to stability studies and the results are given in Table 43, 44.

Table 44: stability study of physical parameters of optimized formulation

PARAMETERS	**INITIAL**	**1ST MONTH**	**2ND MONTH**	**3RD MONTH**
Uniformity of weight *(mg)	400.30±0.1278	400.60±0.1109	400.10±0.1022	400.20±0.1334
Thickness** (mm)	3.850±0.0043	3.870±0.0046	3.855±0.0093	3.850±0.0013
Diameter **(mm)	9.510±0.0139	9.510±0.0190	9.510±0.0203	9.510±0.0237
Hardness**(kg/cm2)	5.29±0.264	5.45±0.227	5.65±0.214	5.30±0.236
Friability* (%)	0.345±0.0029	0.365±0.0090	0.370±0.0019	0.338±0.0034
Floating lag time*** (min)	1.03±0.231	1.09±0.121	1.08±0.045	1.01±0.099
Floating duration***(hours)	12.59±0.023	12.18±0.120	12.72±0.228	12.24±0.083

Mean ±SD (n=20) ** Mean ±SD (n=10) Mean ±SD(n=6)**

Table 44: Assay and Dissolution profile of bilayer floating tablets

Time interval (month)	% Drug content*		Cumulative % release*	
	Rosuvastatin calcium	Propranolol hydrochloride	Rosuvastatin calcium (for 15 mins)	Propranolol hydrochloride (for 12 hours)
1 month	104.30±0.036	101.53±0.021	101.29±0.014	100.01±0.148
2 month	103.50±0.052	101.03±0.036	101.14±0.034	100.31±0.048
3 month	103.79±0.043	101.01±0.024	101.29±0.014	100.20±0.014

***Mean ±SD (n=3)**

No significant changes were observed in the physical appearance, colour and uniformity of weight, hardness, drug content, floating characteristics and drug release of bilayer floating tablets of the optimized batch at 40^0C /75% RH. The bilayer floating tablets are stable.

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

- The present study was aimed to develop regio-selective bilayer floating tablets containing propranolol hydrochloride as SR layer and Rosuvastatin calcium as IR layer for hypertensive patients. Combination therapy of beta-blocker and HMGCo-A Reductase inhibitors is recommended for treatment of hypertensive patients.
- The drug excipient interaction was investigated with FTIR spectroscopy. The study indicated that there was no interaction between the drug and the excipients used in the formulations.
- The floating matrix layer was formulated with hydrophobic polymer (ethyl cellulose) and hydrophilic polymers (HPMC K4M, HPMC K100 and Xanthan gum) to retard the drug release upto 12 hours.
- The rosuvastatin calcium solid dispersion of different ratios (1:1, 1:2, 1:3, and 1:4) was prepared by taking starch phosphate as a novel carrier for the drug.
- From the dissolution results of rosuvastatin solid dispersion, two ratios which exhibit enhanced dissolution of rosuvastatin calcium were selected.
- The immediate release rosuvastatin calcium layer was formulated with sodium starch glycolate (4%).
- All the formulations were evaluated for physical characteristics, drug content, dissolution, release kinetics and stability studies.
- The tablets were formulated by wet granulation method because the flow property of the drugs and the blends were poor.
- The formulated granules were evaluated and showed good flow property.
- The tablets were found to be within the limits with respect to uniformity of weight, hardness, thickness, diameter and friability.
- The disintegration time of the IR tablets containing solid dispersion in ratio of 1:4 and SSG 4 % was found to be optimum.
- The drug content of the formulated IR tablets was found to be within the limits.
- The *invitro* dissolution studies were performed for all the IR-SD formulations. The formulations RC-1, RC-2 and RC-3 released 46.05, 77.79 and 101.29 at the end of 15 minutes. Thus the formulation RC-3 has enhanced solubility of rosuvastatin calcium

and it was optimized formulation and selected for compression with bilayer floating tablets.

- The drug content of the formulated Propranolol hydrochloride SR floating tablets was found to be within Pharmacopoeial limits.
- The drug content of the bilayer floating tablets was estimated by simultaneous estimation method and it was found to be within Pharmacopoeial limits.
- *In vitro* dissolution studies were performed for all the bilayer floating tablet formulations. The formulation RBFT-7 containing HPMC K4M 20% Released the drug upto 12 hours.
- Floating lag time of bilayer floating tablets was within 3 minutes and floating duration was more than 12 hours.
- *In vitro* dissolution study was performed for bilayer floating tablets. At the end of 15 minutes the release was found to be 101.29% for immediate release layer of Rosuvastatin calcium and at the end of 12^{th} hour the release was found to be 101.01 % for sustained release layer of Propranolol hydrochloride.
- Release kinetics of sustained release layer of bilayer floating tablets followed zero order release kinetics. The release of the drug was dependent on diffusion, swelling and erosion of the polymer.
- The stability studies showed that the formulated bilayer floating tablets were stable and did not show any significant changes in the physical characteristics, drug content and dissolution. The results obtained were found to be within acceptable limits. Thus the formulated bilayer floating tablets of propranolol hydrochloride and rosuvastatin calcium was found to be stable.
- Regio- selective bilayer floating tablets of rosuvastatin calcium for immediate release and propranolol hydrochloride for sustained release was formulated to reduce the frequency of administration and to reduce hypertension

FUTURE SCOPE

This work can be extended for

- Permeability improvement of rosuvastatin calcium.
- *Invivo* studies and *invitro- invivo* correlation of regio-selective bilayer floating tablets.
- Clinical studies in healthy volunteers and other biopharmaceutical studies.

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